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(71) Applicant(s):
Cancer Research Technology Limited
(Incorporated in the United Kingdom)
Sardinia House, Sardinia Street, LONDON,
WC2A 3NL, United Kingdom

The Institute of Cancer Research:Royal Cancer Hospital
(Incorporated in the United Kingdom)
123 Old Brompton Road, LONDON,
SW7 3RP, United Kingdom

Astex Therapeutics Limited
(Incorporated in the United Kingdom)
436 Cambridge Science Park, Milton Road,
CAMBRIDGE, CB4 0QA, United Kingdom

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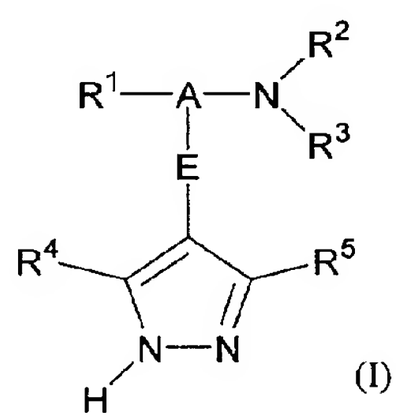
(54) Abstract Title: **Silicon-containing PKB/PKA kinase inhibitors**

(57) The invention provides a compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof; wherein A is a saturated hydrocarbon linker containing 1-7 carbon atoms and having a maximum chain length of 5 atoms between R^1 and NR^2R^3 and a maximum chain length of 4 atoms between E and NR^2R^3, wherein one of the carbon atoms in the linker is replaced by a silicon atom; the silicon atom is substituted by one or two R^{15} substituents; R^{15} is C_{1-4}alkyl, $O(C_{1-4}$alkyl), phenoxy or hydroxyl, wherein the alkyl groups may be substituted with one or more halogen atoms and the phenoxy group may be substituted with one or more halogen or C_{1-4}alkyl groups; or one R^{15} group together with the silicon atom to which it is attached, R^3 and the nitrogen to which it is attached form a 4-7-membered saturated heterocyclic ring; and wherein the Si atom is not adjacent to the NR^2R^3 moiety; E is a mono- or bicyclic carbocyclic or heterocyclic group; and R^1 to R^5 are substituents. The compounds of formula (I) may be useful as PKA/PKB kinase inhibitors e.g. for the treatment of cancer.

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(72) Inventor(s):
Robert George Boyle
David Charles Rees
Robert Downham
Gordon Saxty

(74) Agent and/or Address for Service:
M R Hutchins & Co
23 Mount Sion, TUNBRIDGE WELLS, Kent,
TN1 1TZ, United Kingdom

PHARMACEUTICAL COMPOUNDS

This invention relates to pyrazole-containing aryl- and heteroaryl-alkylamine compounds that inhibit or modulate the activity of protein kinase B (PKB) and protein kinase A (PKA), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by PKB and PKA, and to novel compounds having PKB and PKA inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al.*, *Science,* 253:407-414 (1991); Hiles, *et al.*, *Cell,* 70:419-429 (1992); Kunz, *et al.*, *Cell,* 73:585-596 (1993); Garcia-Bustos, *et al.*, *EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or

regulate the target protein biological function. Phosphorylation of target proteins occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, diseases and conditions of the immune system, diseases and conditions of the central nervous system, and angiogenesis.

Apoptosis or programmed cell death is an important physiological process which removes cells no longer required by an organism. The process is important in early embryonic growth and development allowing the non-necrotic controlled breakdown, removal and recovery of cellular components. The removal of cells by apoptosis is also important in the maintenance of chromosomal and genomic integrity of growing cell populations. There are several known checkpoints in the cell growth cycle at which DNA damage and genomic integrity are carefully monitored. The response to the detection of anomalies at such checkpoints is to arrest the growth of such cells and initiate repair processes. If the damage or anomalies cannot be repaired then apoptosis is initiated by the damaged cell in order to prevent the propagation of faults and errors. Cancerous cells consistently contain numerous mutations, errors or rearrangements in their chromosomal DNA. It is widely believed that this occurs in part because the majority of tumours have a defect in one or more of the processes responsible for initiation of the apoptotic process. Normal control mechanisms cannot kill the cancerous cells and the chromosomal or DNA coding errors continue to be propagated. As a consequence restoring these pro-apoptotic signals or suppressing unregulated survival signals is an attractive means of treating cancer.

The signal transduction pathway containing the enzymes phosphatidylinositol 3-kinase (PI3K), PDK1 and PKB amongst others, has long been known to mediate increased resistance to apoptosis or survival responses in many cells. There is a substantial amount of data to indicate that this pathway is an important survival pathway used by many growth factors to suppress apoptosis. The enzyme PI3K is activated by a range of growth and survival factors e.g. EGF, PDGF and through the generation of polyphosphatidylinositols, initiates the activation of the downstream signalling events including the activity of the kinases PDK1 and protein kinase B (PKB) also known as Akt. This is also true in host tissues, e.g. vascular endothelial cells as well as neoplasias. PKB is a protein ser/thr kinase consisting of a kinase domain together with an N-terminal PH domain and C-terminal regulatory domain. The enzyme PKB itself is phosphorylated on Thr 308 by PDK1 and on Ser 473 by an as yet unidentified kinase. Full activation requires phosphorylation at both sites whilst association between PIP3 and the PH domain is required for anchoring of the enzyme to the cytoplasmic face of the lipid membrane providing optimal access to substrates.

Activated PKB in turn phosphorylates a range of substrates contributing to the overall survival response. Whilst we cannot be certain that we understand all of the factors responsible for mediating the PKB dependent survival response, some important actions are believed to be phosphorylation and inactivation of the pro-apoptotic factor BAD and caspase 9, phosphorylation of Forkhead transcription factors e.g. FKHR leading to their exclusion from the nucleus, and activation of the NfkappaB pathway by phosphorylation of upstream kinases in the cascade.

In addition to the anti-apoptotic and pro-survival actions of the PKB pathway, the enzyme also plays an important role in promoting cell proliferation. This action is again likely to be mediated via several actions, some of which are thought to be phosphorylation and inactivation of the cyclin dependent kinase inhibitor of $p21^{Cip1/WAF1}$, and phosphorylation and activation of mTOR, a kinase controlling several aspects of cell growth.

The phosphatase PTEN which dephosphorylates and inactivates polyphosphatidyl-inositols is a key tumour suppressor protein which normally acts to regulate the PI3K/PKB survival pathway. The significance of the PI3K/PKB pathway in tumourigenesis can be judged from the observation that PTEN is one of the most common targets of mutation in human tumours, with mutations in this phosphatase having been found in ~50% or more of melanomas (Guldberg et al 1997, Cancer Research 57, 3660-3663) and advanced prostate cancers (Cairns et al 1997 Cancer Research 57, 4997). These observations and others suggest that a wide range of tumour types are dependent on the enhanced PKB activity for growth and survival and would respond therapeutically to appropriate inhibitors of PKB.

There are 3 closely related isoforms of PKB called alpha, beta and gamma, which genetic studies suggest have distinct but overlapping functions. Evidence suggests that they can all independently play a role in cancer. For example PKB beta has been found to be over-expressed or activated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19, 2324 – 2330), PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437) and increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532).

The PKB pathway also functions in the growth and survival of normal tissues and may be regulated during normal physiology to control cell and tissue function. Thus disorders associated with undesirable proliferation and survival of normal cells and tissues may also benefit therapeutically from treatment with a PKB inhibitor. Examples of such disorders are disorders of immune cells associated with prolonged expansion and survival of cell population leading to a prolonged or up regulated immune response. For example, T and B lymphocyte response to cognate antigens or growth factors such as interleukin-2 activates the PI3K/PKB pathway and is responsible for maintaining the survival of the antigen specific lymphocyte clones during the immune response. Under conditions in which lymphocytes and

other immune cells are responding to inappropriate self or foreign antigens, or in which other abnormalities lead to prolonged activation, the PKB pathway contributes an important survival signal preventing the normal mechanisms by which the immune response is terminated via apoptosis of the activated cell population. There is a considerable amount of evidence demonstrating the expansion of lymphocyte populations responding to self antigens in autoimmune conditions such as multiple sclerosis and arthritis. Expansion of lymphocyte populations responding inappropriately to foreign antigens is a feature of another set of conditions such as allergic responses and asthma. In summary inhibition of PKB could provide a beneficial treatment for immune disorders.

Other examples of inappropriate expansion, growth, proliferation, hyperplasia and survival of normal cells in which PKB may play a role include but are not limited to atherosclerosis, cardiac myopathy and glomerulonephritis.

In addition to the role in cell growth and survival, the PKB pathway functions in the control of glucose metabolism by insulin. Available evidence from mice deficient in the alpha and beta isoforms of PKB suggests that this action is mediated by the beta isoform. As a consequence, modulators of PKB activity may also find utility in diseases in which there is a dysfunction of glucose metabolism and energy storage such as diabetes, metabolic disease and obesity.

Cyclic AMP-dependent protein kinase (PKA) is a serine/threonine protein kinase that phosphorylates a wide range of substrates and is involved in the regulation of many cellular processes including cell growth, cell differentiation, ion-channel conductivity, gene transcription and synaptic release of neurotransmitters. In its inactive form, the PKA holoenzyme is a tetramer comprising two regulatory subunits and two catalytic subunits.

PKA acts as a link between G-protein mediated signal transduction events and the cellular processes that they regulate. Binding of a hormone ligand such as glucagon to a transmembrane receptor activates a receptor-coupled G-protein (GTP-binding and hydrolyzing protein). Upon activation, the alpha subunit of the G protein

dissociates and binds to and activates adenylate cyclase, which in turn converts ATP to cyclic-AMP (cAMP). The cAMP thus produced then binds to the regulatory subunits of PKA leading to dissociation of the associated catalytic subunits. The catalytic subunits of PKA, which are inactive when associated with the regulatory sub-units, become active upon dissociation and take part in the phosphorylation of other regulatory proteins.

For example, the catalytic sub-unit of PKA phosphorylates the kinase Phosphorylase Kinase which is involved in the phosphorylation of Phosphorylase, the enzyme responsible for breaking down glycogen to release glucose. PKA is also involved in the regulation of glucose levels by phosphorylating and deactivating glycogen synthase. Thus, modulators of PKA activity (which modulators may increase or decrease PKA activity) may be useful in the treatment or management of diseases in which there is a dysfunction of glucose metabolism and energy storage such as diabetes, metabolic disease and obesity.

PKA has also been established as an acute inhibitor of T cell activation. Anndahl *et al,* have investigated the possible role of PKA type I in HIV-induced T cell dysfunction on the basis that T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analogues than are normal T cells. From their studies, they concluded that increased activation of PKA type I may contribute to progressive T cell dysfunction in HIV infection and that PKA type I may therefore be a potential target for immunomodulating therapy.- Aandahl, E. M., Aukrust, P., Skålhegg, B. S., Müller, F., Frøland, S. S., Hansson, V., Taskén, K. *Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients. FASEB J.* 12, 855--862 (1998).

It has also been recognised that mutations in the regulatory sub-unit of PKA can lead to hyperactivation in endocrine tissue.

Because of the diversity and importance of PKA as a messenger in cell regulation, abnormal responses of cAMP can lead to a variety of human diseases such as irregular cell growth and proliferation (Stratakis, C.A.; Cho-Chung, Y.S.; Protein

Kinase A and human diseases. *Trends Endrocri. Metab.* 2002, 13, 50-52). Over-expression of PKA has been observed in a variety of human cancer cells including those from ovarian, breast and colon patients. Inhibition of PKA would therefore be an approach to treatment of cancer (Li, Q.; Zhu, G-D.; *Current Topics in Medicinal Chemistry*, 2002, 2, 939-971).

For a review of the role of PKA in human disease, see for example, *Protein Kinase A and Human Disease*, Edited by Constantine A. Stratakis, Annals of the New York Academy of Sciences, Volume 968, 2002, ISBN 1-57331-412-9.

Several classes of compounds have been disclosed as having PKA and PKB inhibitory activity.

For example, a class of isoquinolinyl-sulphonamido-diamines having PKB inhibitory activity is disclosed in WO 01/91754 (Yissum).

WO 00/07996 (Chiron) discloses substituted pyrazoles having estrogen receptor agonist activity. The compounds are described as being useful in treatingor preventing *inter alia* estrogen-receptor mediated breast cancer. PKB inhibitory activity is not disclosed.

WO 00/31063 (Searle) discloses substituted pyrazole compounds as p38 kinase inhibitors.

WO 01/32653 (Cephalon) discloses a class of pyrazolone kinase inhibitors.WO 03/059884 (X-Ceptor Therapeutics) discloses N-substituted pyridine compounds as modulators of nuclear receptors.

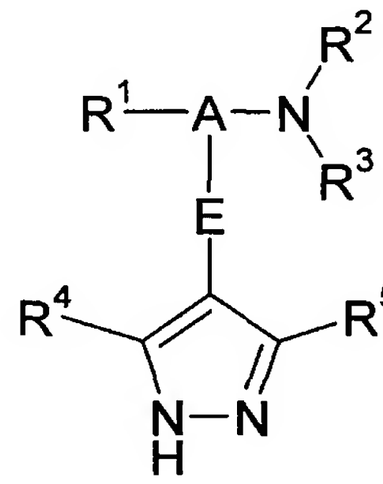
WO 03/068230 (Pharmacia) discloses substituted pyridones as p38 MAP kinase modulators.

WO 00/66562 (Dr Reddy's Research Foundation) discloses a class of 1-phenyl-substituted pyrazoles for use as anti-inflammatory agents. The 1-phenyl group is substituted by a sulphur-containing substituent as a sulphonamide or sulphonyl group.

Summary of the Invention

The invention provides compounds that have protein kinase B (PKB) and protein A (PKA) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by PKB or PKA.

In a first aspect, the invention provides a compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof;

wherein:

A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group is replaced by a silicon atom, wherein the silicon atom is substituted with one or two substituents R^{15}, such that the silicon atom has a quaternary configuration;

each R^{15} is independently C_{1-4} alkyl, $O(C_{1-4}$ alkyl), phenoxy or hydroxy, wherein alkyl groups may be substituted with one or more halogen atoms and the phenoxy group may be substituted with one or more halogen or C_1-C_4 alkyl groups;

or one R^{15} group and the silicon atom to which it is attached and R^3 and the nitrogen to which it is attached form a 4 to 7 membered saturated heterocyclic ring;

and wherein the silicon atom is not adjacent the NR^2R^3 moiety;

and one of the carbon atoms in the linker group A may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may

optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing the Si atom and/or a further heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or

NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

The invention further provides:

- A compound *per se* of the formula (II), (III), (IV), (V) or any other sub-group or embodiment of the formula (I) as defined herein.

- A compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

- The use of a compound of formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

- A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- A method for treating a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, the method comprising administering to the mammal a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein in an amount effective to inhibit protein kinase B activity.

- A method of inhibiting protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase B using a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- A compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

- The use of a compound of formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

- A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a subject in need thereof a compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein.

- A method for treating a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, the method comprising administering to the mammal a compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein in an amount effective to inhibit protein kinase A activity.

- A method of inhibiting protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein.

- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase A using a compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein.

- The use of a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth or abnormally arrested cell death.

- A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein in an amount effective in inhibiting abnormal cell growth or abnormally arrested cell death.

- A method for alleviating or reducing the incidence of a disease or condition comprising or arising from abnormal cell growth or abnormally arrested cell death in a mammal, which method comprises administering to the mammal a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein in an amount effective in inhibiting abnormal cell growth.

- A pharmaceutical composition comprising a novel compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein and a pharmaceutically acceptable carrier.

- A compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for use in medicine.

- The use of a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for the manufacture of a medicament for the prophylaxis or treatment of any one of the disease states or conditions disclosed herein.

- A method for the treatment or prophylaxis of any one of the disease states or conditions disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- A method for alleviating or reducing the incidence of a disease state or condition disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- A method for the diagnosis and treatment of a disease state or condition mediated by protein kinase B, which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against protein kinase B; and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein.

- The use of a compound of the formula (I), (II), (III), (IV), (V) or any sub-group thereof as defined herein for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase B.

- A method for the diagnosis and treatment of a disease state or condition mediated by protein kinase A, which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against protein kinase A; and (ii) where it is

indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein.

- The use of a compound of the formula (I), (II), (III), (IV), (V) or any sub-group or embodiment thereof as defined herein for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against protein kinase A.

General Preferences and Definitions

The following general preferences and definitions shall apply to each of the moieties A, E and R^1 to R^5, R^9, R^{15} and any sub-definition, sub-group or embodiment thereof, unless the context indicates otherwise.

Any references to Formula (I) herein shall be taken also to refer any sub-group of compounds within formula (I) unless the context requires otherwise.

References to "carbocyclic" and "heterocyclic" groups as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. In general, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7, and 8 ring members, more usually 3 to 7, and preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and

the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or by a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined herein.

The term non-aromatic group embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups.

Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

A bicyclic heteroaryl group may be, for example, a group selected from:

a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

b) a pyridine ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

c) a pyrimidine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

d) a pyrrole ring fused to a a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

e) a pyrazole ring fused to a a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

f) a pyrazine ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

g) an imidazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

h) an oxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

i) an isoxazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

j) a thiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

k) an isothiazole ring fused to a 5- or 6-membered ring containing 1 or 2 ring heteroatoms;

l) a thiophene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

m) a furan ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;

n) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and

o) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

Examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole and pyrazolopyridine groups.

Examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline and indane groups.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur.

The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine). Other examples of non-aromatic heterocyclic groups include cyclic amide moieties (e.g. as in pyrrolidone) and cyclic ester moieties (e.g. as in butyrolactone).

Examples of monocyclic non-aromatic heterocyclic groups include 5-, 6-and 7-membered monocyclic heterocyclic groups. Particular examples include morpholine, thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine), piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), N-alkyl piperidines such as N-methyl piperidine, piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine, N-ethyl piperazine and N-isopropylpiperazine.

One sub-group of monocyclic non-aromatic heterocyclic groups includes morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone,

oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines. A further particular example of a non-aromatic heterocyclic group, which also forms part of the above group of preferred non-aromatic heterocyclic groups, is azetidine.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalinyl.

Each of the definitions of carbocyclic and heterocyclic groups in this specification may optionally exclude any one or any combination of two or more of the following moieties:

- substituted or unsubstituted pyridone rings;
- substituted or unsubstituted pyrrolo[1,2-a]pyrimid-4-ones;
- substituted or unsubstituted pyrazolones.

Where reference is made herein to carbocyclic and heterocyclic groups, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group

may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

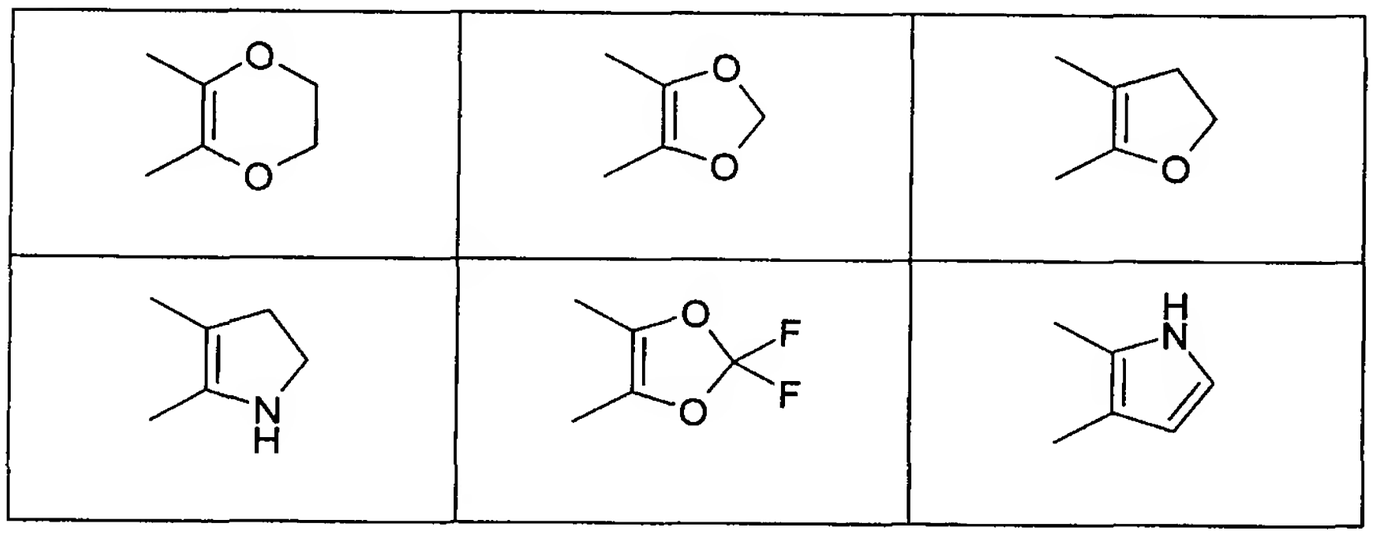
X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10}. In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

The substituents R^{10} may be selected such that they contain no more than 20 non-hydrogen atoms, for example, no more than 15 non-hydrogen atoms, e.g. no more than 12, or 10, or 9, or 8, or 7, or 6, or 5 non-hydrogen atoms.

Where the carbocyclic and heterocyclic groups have a pair of substituents on adjacent ring atoms, the two substituents may be linked so as to form a cyclic group. For example, an adjacent pair of substituents on adjacent carbon atoms of a ring may be linked via one or more heteroatoms and optionally substituted alkylene groups to form a fused oxa-, dioxa-, aza-, diaza- or oxa-aza-cycloalkyl group.

Examples of such linked substituent groups include:



Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of hydrocarbyl groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or, where stated, can be substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl

groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl, naphthyl, indane and indene groups.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

When present, and where stated, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituted hydrocarbyl group can be a partially fluorinated or perfluorinated group such as difluoromethyl or

trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

Where stated, one or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ (or a sub-group thereof) wherein X^1 and X^2 are as hereinbefore defined, provided that at least one carbon atom of the hydrocarbyl group remains. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. In general, the number of linear or backbone carbon atoms replaced will correspond to the number of linear or backbone atoms in the group replacing them. Examples of groups in which one or more carbon atom of the hydrocarbyl group have been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C-C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2), amines (C replaced by NR^c). Further examples include ureas, carbonates and carbamates (C-C-C replaced by $X^1C(X^2)X^1$).

Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members.

The definition "R^a-R^b" as used herein, either with regard to substituents present on a carbocyclic or heterocyclic moiety, or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, C(S) NR^c, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)$ NR^c, $OC(S)NR^c$, SC(S) NR^c,

$NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^cNR^c$, S, SO, SO_2, NR^c, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined. Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

When R^a is O and R^b is a C_{1-8} hydrocarbyl group, R^a and R^b together form a hydrocarbyloxy group. Preferred hydrocarbyloxy groups include saturated hydrocarbyloxy such as alkoxy (e.g. C_{1-6} alkoxy, more usually C_{1-4} alkoxy such as ethoxy and methoxy, particularly methoxy), cycloalkoxy (e.g. C_{3-6} cycloalkoxy such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy) and cycloalkyalkoxy (e.g. C_{3-6} cycloalkyl-C_{1-2} alkoxy such as cyclopropylmethoxy).

The hydrocarbyloxy groups can be substituted by various substituents as defined herein. For example, the alkoxy groups can be substituted by halogen (e.g. as in difluoromethoxy and trifluoromethoxy), hydroxy (e.g. as in hydroxyethoxy), C_{1-2} alkoxy (e.g. as in methoxyethoxy), hydroxy-C_{1-2} alkyl (as in hydroxyethoxyethoxy) or a cyclic group (e.g. a cycloalkyl group or non-aromatic heterocyclic group as hereinbefore defined). Examples of alkoxy groups bearing a non-aromatic heterocyclic group as a substituent are those in which the heterocyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkoxy group is a C_{1-4} alkoxy group, more typically a C_{1-3} alkoxy group such as methoxy, ethoxy or n-propoxy.

Alkoxy groups may be substituted by, for example, a monocyclic group such as pyrrolidine, piperidine, morpholine and piperazine and N-substituted derivatives thereof such as N-benzyl, N-C_{1-4} acyl and N-C_{1-4} alkoxycarbonyl. Particular examples include pyrrolidinoethoxy, piperidinoethoxy and piperazinoethoxy.

When R^a is a bond and R^b is a C_{1-8} hydrocarbyl group, examples of hydrocarbyl groups R^a-R^b are as hereinbefore defined. The hydrocarbyl groups may be saturated groups such as cycloalkyl and alkyl and particular examples of such groups include methyl, ethyl and cyclopropyl. The hydrocarbyl (e.g. alkyl) groups can be substituted by various groups and atoms as defined herein. Examples of substituted alkyl groups include alkyl groups substituted by one or more halogen atoms such as fluorine and chlorine (particular examples including bromoethyl, chloroethyl, difluoromethyl, 2,2,2-trifluoroethyl and perfluoroalkyl groups such as trifluoromethyl), or hydroxy (e.g. hydroxymethyl and hydroxyethyl), C_{1-8} acyloxy (e.g. acetoxymethyl and benzyloxymethyl), amino and mono- and dialkylamino (e.g. aminoethyl, methylaminoethyl, dimethylaminomethyl, dimethylaminoethyl and *tert*-butylaminomethyl), alkoxy (e.g. C_{1-2} alkoxy such as methoxy – as in methoxyethyl), and cyclic groups such as cycloalkyl groups, aryl groups, heteroaryl groups and non-aromatic heterocyclic groups as hereinbefore defined).

Particular examples of alkyl groups substituted by a cyclic group are those wherein the cyclic group is a saturated cyclic amine such as morpholine, piperidine, pyrrolidine, piperazine, C_{1-4}-alkyl-piperazines, C_{3-7}-cycloalkyl-piperazines, tetrahydropyran or tetrahydrofuran and the alkyl group is a C_{1-4} alkyl group, more typically a C_{1-3} alkyl group such as methyl, ethyl or n-propyl. Specific examples of alkyl groups substituted by a cyclic group include pyrrolidinomethyl, pyrrolidinopropyl, morpholinomethyl, morpholinoethyl, morpholinopropyl, piperidinylmethyl, piperazinomethyl and N-substituted forms thereof as defined herein.

Particular examples of alkyl groups substituted by aryl groups and heteroaryl groups include benzyl, phenethyl and pyridylmethyl groups.

When R^a is SO_2NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is SO_2NR^c include aminosulphonyl, C_{1-4} alkylaminosulphonyl and di-C_{1-4} alkylaminosulphonyl groups, and sulphonamides formed from a cyclic amino group

such as piperidine, morpholine, pyrrolidine, or an optionally N-substituted piperazine such as N-methyl piperazine.

Examples of groups R^a-R^b where R^a is SO_2 include alkylsulphonyl, heteroarylsulphonyl and arylsulphonyl groups, particularly monocyclic aryl and heteroaryl sulphonyl groups. Particular examples include methylsulphonyl, phenylsulphonyl and toluenesulphonyl.

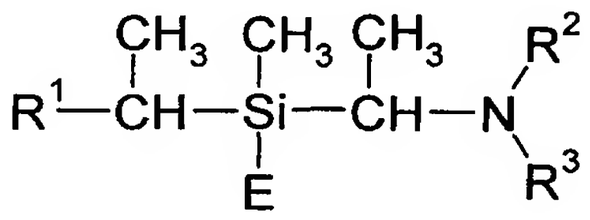
When R^a is NR^c, R^b can be, for example, hydrogen or an optionally substituted C_{1-8} hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is NR^c include amino, C_{1-4} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, *tert*-butylamino), di-C_{1-4} alkylamino (e.g. dimethylamino and diethylamino) and cycloalkylamino (e.g. cyclopropylamino, cyclopentylamino and cyclohexylamino).

Specific Embodiments of and Preferences for A, E, R^1 to R^5, R^9 and R^{15}

The Group "A"

In formula (I), A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3. Within these constraints, the moieties E and R^1 can each be attached at any location on the group A.

The term "maximum chain length" as used herein refers to the number of atoms lying directly between the two moieties in question, and does not take into account any branching in the chain or any hydrogen atoms that may be present. For example, in the structure A shown below:



(A)

the chain length between R^1 and NR^2R^3 is 3 atoms whereas the chain length between E and NR^2R^3 is 2 atoms.

In general it is presently preferred that the linker group has a maximum chain length of 3 atoms (for example 1 or 2 atoms).

In one embodiment, the linker group has a chain length of 2 atoms extending between R^1 and NR^2R^3.

In another embodiment, the linker group has a chain length of 3 atoms extending between R^1 and NR^2R^3.

It is preferred that the linker group has a maximum chain length of 3 atoms extending between E and NR^2R^3.

In one particularly preferred group of compounds, the linker group has a chain length of 2 or 3 atoms extending between R^1 and NR^2R^3 and a chain length of 2 or 3 atoms extending between E and NR^2R^3.

It is particularly preferred that there is only one atom of the linker group A between E and R^1.

One of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom.

When present, the nitrogen atom may be linked directly to the group E.

In one embodiment, the carbon atom to which the group R^1 is attached is replaced by an oxygen atom.

In another embodiment, R^1 and E are attached to the same atom of the linker group, and a carbon atom in the chain extending between E and NR^2R^3 is replaced by an oxygen atom.

When a nitrogen atom or oxygen atom are present, it is preferred that the nitrogen or oxygen atom and the NR^2R^3 group are spaced apart by at least two intervening carbon atoms.

The carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group is not located at a carbon atom α with respect to the NR^2R^3 group, and provided also that the oxo group is located at a carbon atom α with respect to the NR^2R^3 group. Typically, the hydroxy group, if present, is located at a position β with respect to the NR^2R^3 group. In general, no more than one hydroxy group will be present. Where fluorine is present, it may be present as a single fluorine substituent or may be present in a difluoromethylene or trifluoromethyl group, for example. In one embodiment, a fluorine atom is located at a position β with respect to the NR^2R^3 group.

It will be appreciated that that when an oxo group is present at the carbon atom adjacent the NR^2R^3 group, the compound of the formula (I) will be an amide.

In one embodiment of the invention, no fluorine atoms are present in the linker group A.

In another embodiment of the invention, no hydroxy groups are present in the linker group A.

In a further embodiment, no oxo group is present in the linker group A.

In one group of compounds of the formula (I) neither hydroxy groups nor fluorine atoms are present in the linker group A, e.g. the linker group A is unsubstituted.

Preferably, when a carbon atom in the linker group A is replaced by a nitrogen atom, the group A bears no more than one hydroxy substituent and more preferably bears no hydroxy substituents.

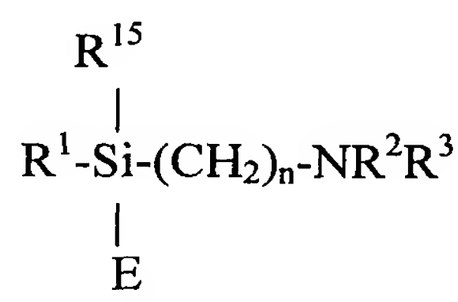
When there is a chain length of four atoms between E and NR^2R^3, it is preferred that the linker group A contains no nitrogen atoms and more preferably has an all carbon skeleton.

In order to modify the susceptibility of the compounds to metabolic degradation *in vivo*, the linker group A can have a branched configuration at the carbon atom attached to the NR^2R^3 group. For example, the carbon atom attached to the NR^2R^3 group can be attached to a pair of *gem*-dimethyl groups.

In one particular group of compounds of the formula (I), the silicon atom is linked directly to the group E and is substituted by a single group R^{15}.

In one variation of this group of compounds, R^{15} and R^3 together with the silicon and nitrogen atoms to which they are attached form a 5 to 7 membered saturated ring. Compounds in which R^{15} and R^3 form a 6-membered ring are especially preferred.

In another variation of this group of compounds, R^{15} is C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy and there are 1, 2 or 3 further carbon atoms between the Si and the NR^2R^3 moiety. In this case, it is preferred that the linker A is of the form:

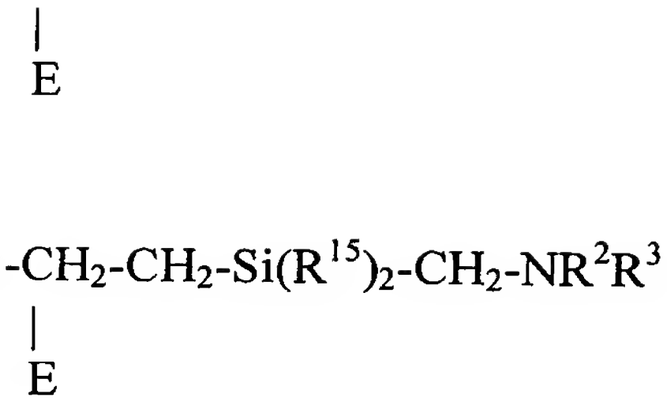


where n is 1, 2 or 3; and

where R^1, E and NR^2R^3 are not part of linker A but are included to show the position of the linker A within the compound of formula (I).

In another particular group of compounds, the silicon atom in the linker A is between the group E and the NR^2R^3 moiety but is not directly linked to the group E. Preferred linkers A of this type are of the form:

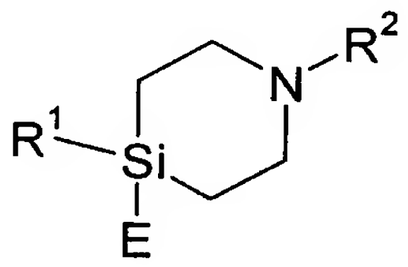
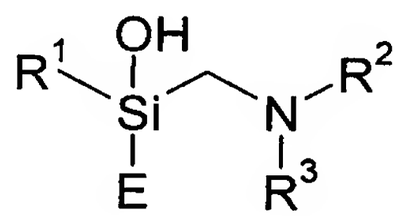
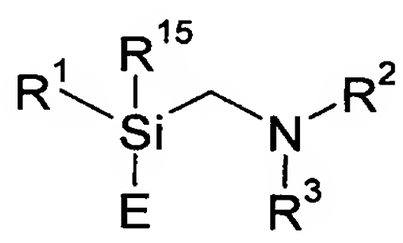
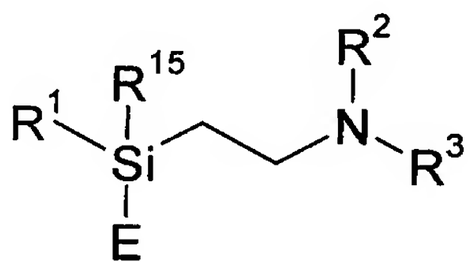
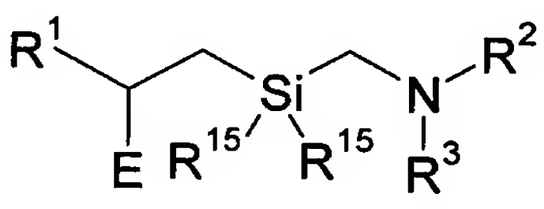
R^1-CH_2- $Si(R^{15})_2$-CH_2-CH_2-NR^2R^3 or



where R^1, E and NR^2R^3 are not part of linker A but are included to show the position of the linker A within the compound of formula (I).

Particular examples of the linker group A, together with their points of attachment to the groups R^1, E and NR^2R^3, are shown in Table 1 below.

Table 1:

 A1	 A2	 A3
 A4	 A5	

R^1

The group R^1 is an aryl or heteroaryl group and may be selected from the list of such groups set out in the section headed General Preferences and Definitions.

R^1 can be monocyclic or bicyclic and, in one preferred embodiment, is monocyclic. Particular examples of monocyclic aryl and heteroaryl groups are six membered aryl and heteroaryl groups containing up to 2 nitrogen ring members, and five membered heteroaryl groups containing up to 3 heteroatom ring members selected from O, S and N.

Examples of such groups include phenyl, naphthyl, thienyl, furan, pyrimidine and pyridine, with phenyl being presently preferred.

The group R^1 can be unsubstituted or substituted by up to 5 substituents, and examples of substituents are those listed in group R^{10} above.

Particular substituents include hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; $CONH_2$; nitro; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy, carboxy or hydroxy; C_{1-4} acylamino; benzoylamino; pyrrolidinocarbonyl; piperidinocarbonyl; morpholinocarbonyl; piperazinocarbonyl; five and six membered heteroaryl and heteroaryloxy groups containing one or two heteroatoms selected from N, O and S; phenyl; phenyl-C_{1-4} alkyl; phenyl-C_{1-4} alkoxy; heteroaryl-C_{1-4} alkyl; heteroaryl-C_{1-4} alkoxy and phenoxy, wherein the heteroaryl, heteroaryloxy, phenyl, phenyl-C_{1-4} alkyl, phenyl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkyl, heteroaryl-C_{1-4} alkoxy and phenoxy groups are each optionally substituted with 1, 2 or 3 substituents selected from C_{1-2} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, $CONH_2$, C_{1-2} hydrocarbyloxy and C_{1-2} hydrocarbyl each optionally substituted by methoxy or hydroxy.

Preferred substituents include hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy or hydroxy; C_{1-4} acylamino; benzoylamino; pyrrolidinocarbonyl; piperidinocarbonyl; morpholinocarbonyl; piperazinocarbonyl; five and six membered heteroaryl groups containing one or two heteroatoms selected from N, O and S, the heteroaryl groups being optionally substituted by one or more C_{1-4} alkyl substituents; phenyl; pyridyl; and phenoxy wherein the phenyl,

pyridyl and phenoxy groups are each optionally substituted with 1, 2 or 3 substituents selected from C_{1-2} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-2} hydrocarbyloxy and C_{1-2} hydrocarbyl each optionally substituted by methoxy or hydroxy.

In one sub-group of compounds, the substituents for R^1 are chosen from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy or hydroxy.

Although up to 5 substituents may be present, more typically there are 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1 or 2.

In one embodiment, the group R^1 is unsubstituted or substituted by up to 5 substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy or hydroxy.

In a further embodiment, the group R^1 can have one or two substituents selected from hydroxy, fluorine, chlorine, cyano, phenyloxy, pyrazinyloxy, benzyloxy, methyl and methoxy.

In another embodiment, the group R^1 can have one or two substituents selected from fluorine, chlorine, trifluoromethyl, methyl and methoxy.

When R^1 is a phenyl group, particular examples of substituent combinations include mono-chlorophenyl and dichlorophenyl.

Further examples of substituent combinations include those wherein R^1 is hydroxyphenyl, fluorochlorophenyl, cyanophenyl, methoxyphenyl, methoxy-chlorophenyl, fluorophenyl, difluorophenyl, phenoxyphenyl, pyrazinyloxyphenyl or benzyloxyphenyl.

When R^1 is a six membered aryl or heteroaryl group, a substituent may advantageously be present at the *para* position on the six-membered ring. Where a substituent is present at the *para* position, it is preferably larger in size than a fluorine atom.

R^2 and R^3

In one group of compounds of the formula (I), R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy.

When the hydrocarbyl moiety is substituted by a hydroxy, amino, methylamino, dimethylamino or methoxy group, typically there are at least two carbon atoms between the substituent and the nitrogen atom of the group NR^2R^3. Particular examples of substituted hydrocarbyl groups are hydroxyethyl and hydroxypropyl.

In another group of compounds of the invention, R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl.

Typically the hydrocarbyl group, whether substituted or unsubstituted, is an alkyl group, more usually a C_1, C_2 or C_3 alkyl group, and preferably a methyl group. In one particular sub-group of compounds, R^2 and R^3 are independently selected from hydrogen and methyl and hence NR^2R^3 can be an amino, methylamino or dimethylamino group. In one particular embodiment, NR^2R^3 can be an amino group. In another particular embodiment, NR^2R^3 can be a methylamino group.

In an alternative embodiment, the C_{1-4} hydrocarbyl group can be a cyclopropyl, cyclopropylmethyl or cyclobutyl group.

In another group of compounds, R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

In a further group of compounds, R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

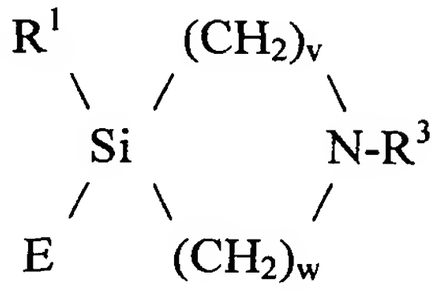
The saturated monocyclic heterocyclic group can be unsubstituted or substituted by one or more substituents R^{10} as defined above in the General Preferences and Definitions section of this application. Typically, however, any substituents on the heterocyclic group will be relatively small substituents such as C_{1-4} hydrocarbyl (e.g. methyl, ethyl, *n*-propyl, *i*-propyl, cyclopropyl, *n*-butyl, *sec*-butyl and *tert*-butyl), fluorine, chlorine, hydroxy, amino, methylamino, ethylamino and dimethylamino. Particular substituents are methyl groups.

The saturated monocyclic ring can be an azacycloalkyl group such as an azetidine, pyrrolidine, piperidine or azepane ring, and such rings are typically unsubstituted. Alternatively, the saturated monocyclic ring can contain an additional heteroatom selected from O and N, and examples of such groups include morpholine and piperazine. Where an additional N atom is present in the ring, this can form part of an NH group or an N-C_{1-4}alkyl group such as an N-methyl, N-ethyl, N-propyl or N-isopropyl group.

Where NR^2R^3 forms an imidazole group, the imidazole group can be unsubstituted or substituted, for example by one or more relatively small substituents such as C_{1-4} hydrocarbyl (e.g. methyl, ethyl, propyl, cyclopropyl and butyl), fluorine, chlorine, hydroxy, amino, methylamino, ethylamino and dimethylamino. Particular substituents are methyl groups.

In a further group of compounds, one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

Examples of such compounds include compounds wherein NR^2R^3 and A form a cyclic group of the formula:



where v and w are each 2 or 3 but cannot both be 3. Particular examples of cyclic compounds are those in which v and w are both 2.

R^4

In formula (I), R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3.

More typically, R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano and CF_3. Preferred values for R^4 include hydrogen and methyl. In a particular embodiment, R^4 is hydrogen.

R^5

In formula (I), R^5 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$; $NHCONHR^9$ where R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is an optionally substituted monocyclic or bicyclic group which may be carbocyclic or heterocyclic.

Examples of carbocyclic and heterocyclic groups are set out above in the General Preferences and Definitions section.

Typically the carbocyclic and heterocyclic groups are monocyclic.

Preferably the carbocyclic and heterocyclic groups are aromatic.

Particular examples of the group R^9 are optionally substituted phenyl or benzyl.

Preferably, R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

More preferably, R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

The group R^9 is typically unsubstituted phenyl or benzyl, or phenyl or benzyl substituted by 1,2 or 3 substituents selected from halogen; hydroxy; trifluoromethyl; cyano; carboxy; C_{1-4}alkoxycarbonyl; C_{1-4} acyloxy; amino; mono- or di-C_{1-4} alkylamino; C_{1-4} alkyl optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; C_{1-4} alkoxy optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; phenyl, five and six membered heteroaryl groups containing up to 3 heteroatoms selected from O, N and S; and saturated carbocyclic and heterocyclic groups containing up to 2 heteroatoms selected from O, S and N.

Particular examples of the moiety R^5 include hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9b}$ and $NHCONHR^{9b}$ where R^{9b} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy (e.g. alkoxy) and C_{1-4} hydrocarbyl (e.g. alkyl) optionally substituted by C_{1-2} alkoxy or hydroxy.

Preferred examples of R^5 include hydrogen, methyl and cyano. Preferably R^5 is hydrogen or methyl.

<u>The Group "E"</u>

In formula (I), E is a monocyclic or bicyclic carbocyclic or heterocyclic group and can be selected from the groups set out above in the section headed General Preferences and Definitions.

Preferred groups E are monocyclic and bicyclic aryl and heteroaryl groups and, in particular, groups containing a six membered aromatic or heteroaromatic ring such as a phenyl, pyridine, pyrazine, pyridazine or pyrimidine ring, more particularly a phenyl, pyridine, pyrazine or pyrimidine ring, and more preferably a pyridine or phenyl ring.

Examples of bicyclic groups include benzo-fused and pyrido-fused groups wherein the group A and the pyrazole ring are both attached to the benzo- or pyrido- moiety.

In one embodiment, E is a monocyclic group.

Particular examples of monocyclic groups include monocyclic aryl and heteroaryl groups such as phenyl, thiophene, furan, pyrimidine, pyrazine and pyridine, phenyl being presently preferred.

One subset of monocyclic aryl and heteroaryl groups comprises phenyl, thiophene, furan, pyrimidine and pyridine.

Examples of non-aromatic monocyclic groups include cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

It is preferred that the group A and the pyrazole group are not attached to adjacent ring members of the group E. For example, the pyrazole group can be attached to the group E in a *meta* or *para* relative orientation. Examples of such groups E include 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl. Further examples include 1,3-disubstituted five membered rings .

The groups E can be unsubstituted or can have up to 4 substituents R^8 which may be selected from the group R^{10} as hereinbefore defined. More typically however, the substituents R^8 are selected from hydroxy; oxo (when E is non-aromatic); halogen

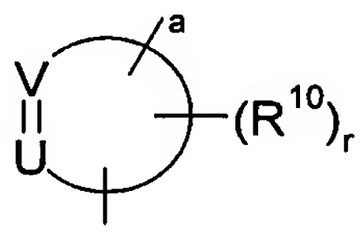
(e.g. chlorine and bromine); trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy optionally substituted by C_{1-2} alkoxy or hydroxy; and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

Preferably there are 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent. In one embodiment, the group E is unsubstituted.

E may be other than:

- a substituted pyridone group;
- a substituted thiazole group;
- a substituted or unsubstituted pyrazole or pyrazolone group;
- a substituted or unsubstituted bicyclic fused pyrazole group;
- a phenyl ring fused to a thiophene ring or a six membered nitrogen-containing heteroaryl ring fused to a thiophene ring;
- a substituted or unsubstituted piperazine group;

The group E can be an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

r is 0, 1 or 2;

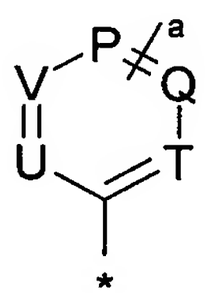
U is selected from N and CR^{12a}; and

V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten;

or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is as hereinbefore defined.

In one preferred group of compounds, E is a group:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

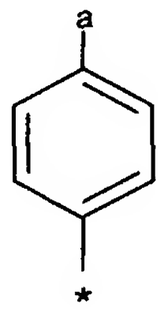
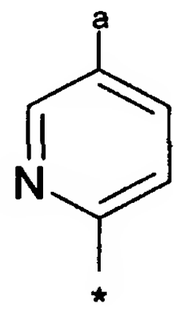
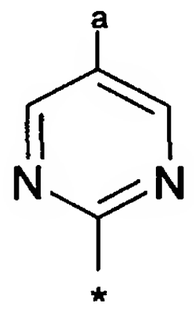
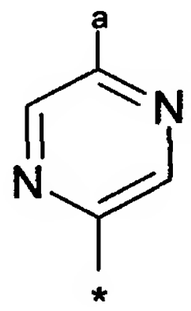
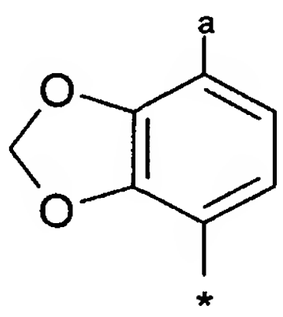
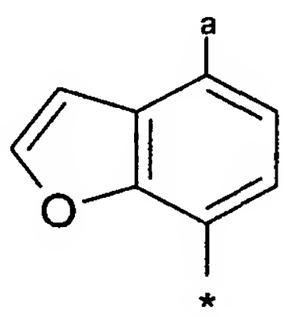
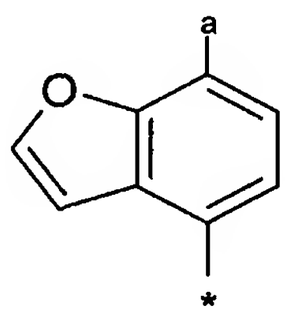
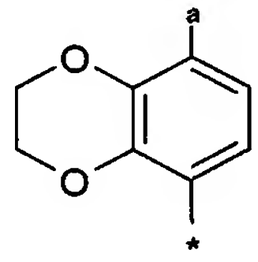
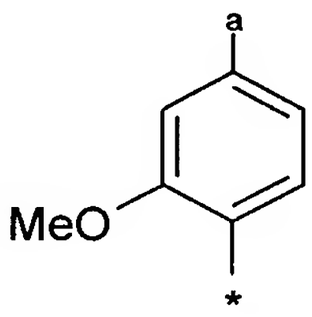
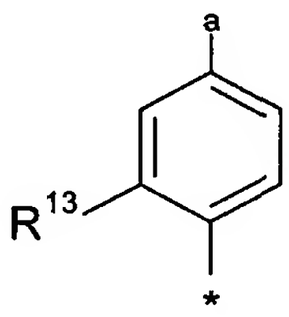
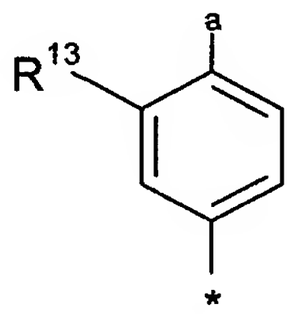
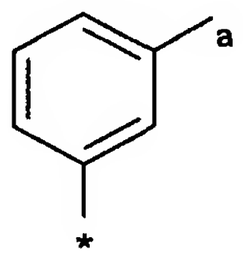
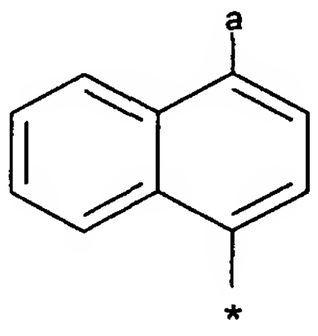
P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom; and U, V and R^{10} are as hereinbefore defined.

Examples of R^{12a} and R^{12b} include hydrogen and substituent groups R^{10} as hereinbefore defined having no more than ten non-hydrogen atoms. Particular examples of R^{12a} and R^{12b} include methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, fluorine, chlorine, methoxy, trifluoromethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethyl, cyano, amino, methylamino, dimethylamino, $CONH_2$, CO_2Et, CO_2H, acetamido, azetidinyl, pyrrolidino, piperidine, piperazino, morpholino, methylsulphonyl, aminosulphonyl, mesylamino and trifluoroacetamido.

Preferably, when U is CR^{12a} and/or V is CR^{12b} the atoms or groups in R^{12a} and R^{12b} that are directly attached to the carbon atom ring members C are selected from H, O (e.g. as in methoxy), NH (e.g. as in amino and methylamino) and CH_2 (e.g. as in methyl and ethyl).

Particular examples of the linker group E, together with their points of attachment to the group A (^{a}) and the pyrazole ring (*) are shown in Table 2 below.

Table 2:

 B1	 B2	 B3	 B4
 B5	 B6	 B7	 B8
 B9	 B10	 B11	 B12
 B13			

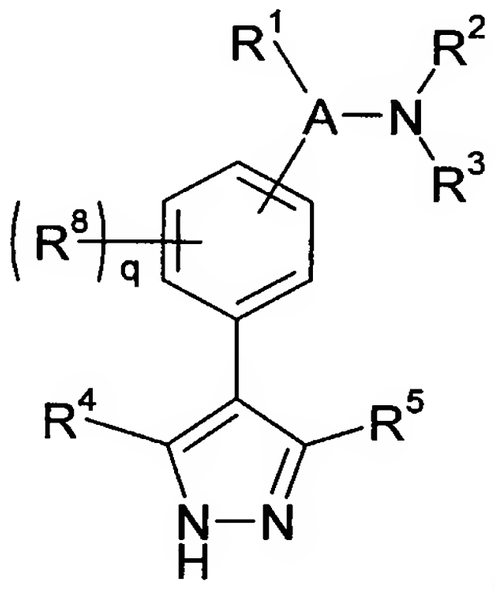
In the table, the substituent group R^{13} is selected from methyl, chlorine, fluorine and trifluoromethyl.

The following optional exclusions may apply to the definition of E in any of formulae (I), (Ia), (Ib), (II), (III), (IV) and (V) and any sub-groups or sub-definitions thereof as defined herein:

- E may be other than a phenyl group having a sulphur atom attached to the position *para* with respect to the pyrazole group.

- E may be other than a substituted or unsubstituted benzimidazole, benzoxazole or benzthiazole group.

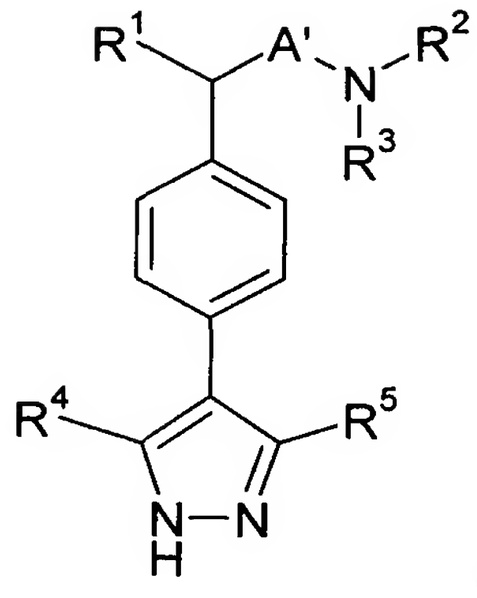
One sub-group of compounds of the formula (I) has the general formula (II):



(II)

wherein the group A is attached to the *meta* or *para* position of the benzene ring, q is 0-4; R^1, R^2, R^3, R^4 and R^5 are as defined herein in respect of formula (I) and sub-groups, examples and preferences thereof; and R^8 is a substituent group as hereinbefore defined. In formula (II), q is preferably 0, 1 or 2, more preferably 0 or 1 and most preferably 0. Preferably the group A is attached to the *para* position of the benzene ring.

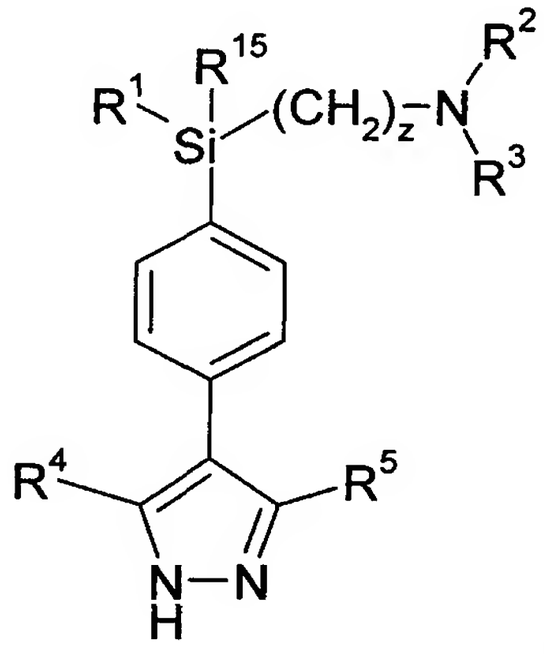
Within formula (II), one particular sub-group of compounds of the invention is represented by the formula (III):



(III)

where A' is the residue of the group A and R^1 to R^5 are as defined herein.

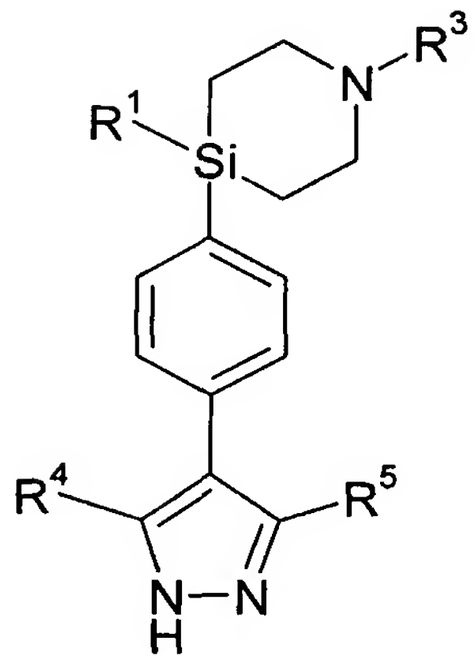
Within formula (III), one preferred group of compounds is presented by the formula (IV):



(IV)

wherein z is 1 or 2 and R^1 to R^5 and R^{15} are as defined herein.

Another group of compounds within formula (III) is represented by formula (V):



(V)

wherein and R^1 and R^3 to R^5 are as defined herein.

In formula (V), R^3 is preferably selected from hydrogen and C_{1-4} hydrocarbyl, for example C_{1-4} alkyl such as methyl, ethyl and isopropyl. More preferably R^3 is hydrogen.

In each of formulae (II) to (V), R^1 is preferably an optionally substituted phenyl group as defined herein.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or R^3 and/or R^4 and/or R^5 and/or R^9 and that all such combinations are embraced by this application.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are as illustrated in the examples below and are selected from:

4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
1-methyl-4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
4-(4-Chloro-phenyl)- 4'-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
and salts, solvates, tautomers and N-oxides thereof.

Salts, Solvates, Tautomers, Isomers, N-Oxides, Esters, Prodrugs and Isotopes

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) included references to formulae (II), (III), (IV) and (V) and all other sub-groups, preferences and examples thereof as defined herein.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms thereof, for example, as discussed below.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds. As in the preceding sections of this application, all references to formula (I) should be taken to refer also to formula (II) and sub-groups thereof unless the context indicates otherwise.

Salt forms may be selected and prepared according to methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. For example, acid addition salts may be prepared by dissolving the free base in an organic solvent in which a given salt form is insoluble or poorly soluble and then adding the required acid in an appropriate solvent so that the salt precipitates out of solution.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1*S*)-camphor-10-sulphonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic, (±)-DL-mandelic, methanesulphonic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, toluenesulphonic (e.g. *p*-toluenesulphonic), undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

One particular group of acid addition salts includes salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

Another group of acid addition salts includes salts formed from acetic, adipic, ascorbic, aspartic, citric, DL-Lactic, fumaric, gluconic, glucuronic, hippuric, hydrochloric, glutamic, DL-malic, methanesulphonic, sebacic, stearic, succinic and tartaric acids.

The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed. In stronger acids, the basic pyrazole nitrogen, as well as the nitrogen atom in the group NR^2R^3, may take part in salt formation. For example, where the acid has a pKa of less than about 3 (e.g. an acid

such as hydrochloric acid, sulphuric acid or trifluoroacetic acid), the compounds of the invention will typically form salts with 2 molar equivalents of the acid.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

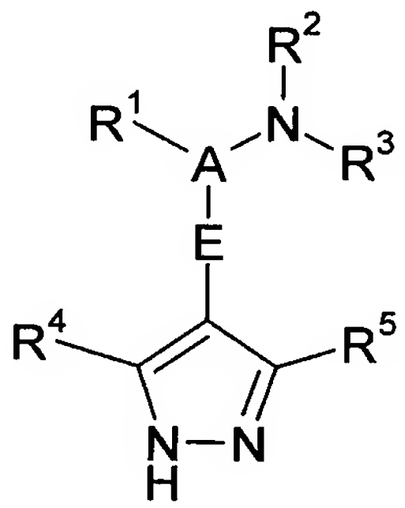
Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley

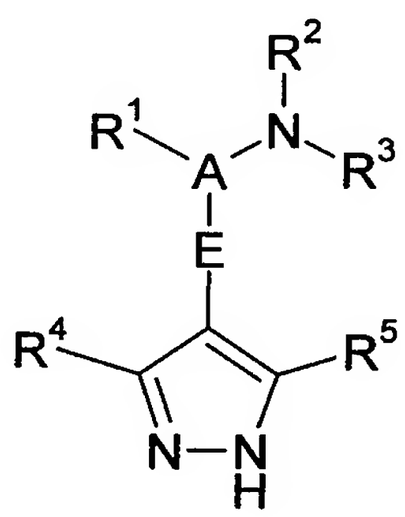
Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

For example, in compounds of the formula (I) the pyrazole group may take either of the following two tautomeric forms A and B.



A



B

For simplicity, the general formula (I) illustrates form A but the formula is to be taken as embracing both form A and form B.

Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers and diastereoisomers), either as individual optical isomers, or mixtures or two or more optical isomers, unless the context requires otherwise.

For example, the group A can include one or more chiral centres. Thus, when E and R^1 are both attached to the same carbon atom on the linker group A, the said

carbon atom is typically chiral and hence the compound of the formula (I) will exist as a pair of enantiomers (or more than one pair of enantiomers where more than one chiral centre is present in the compound).

The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluloyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the

formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). In one embodiment of the invention, formula (I) includes within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. In another embodiment of the invention, formula (I) does not include within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:

C_{1-7}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);

C_{1-7} aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl;

2-(4-morpholino)ethyl); and

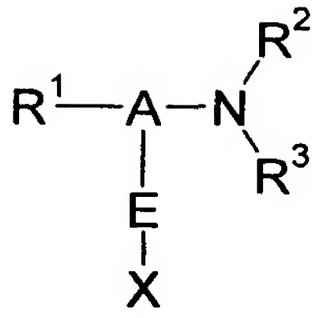
acyloxy-C_{1-7}alkyl (e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)-carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)-carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT) and ligand-directed enzyme pro-drug therapy (LIDEPT). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

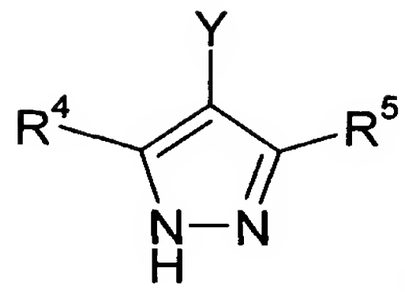
Methods for the preparation of compounds of the formula (I)

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) included references to formulae (Ia), (Ib), (II), (III), (IV) and (V) and all other sub-groups, preferences and examples thereof as defined herein.

Compounds of the formula (I) can be prepared by reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



(X)



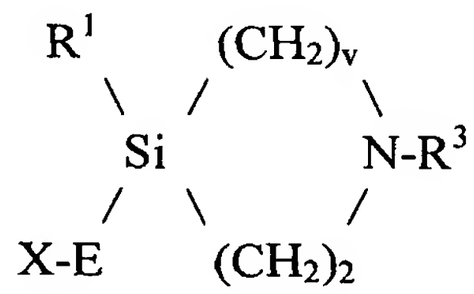
(XI)

wherein A, E, and R^1 to R^5 are as hereinbefore defined, one of the groups X and Y is chlorine, bromine or iodine or a trifluoromethanesulphonate (triflate) group, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue.

The reaction can be carried out under typical Suzuki Coupling conditions in the presence of a palladium catalyst such as bis(tri-*t*-butylphosphine)palladium and a base (e.g. a carbonate such as potassium carbonate). The reaction may be carried out in an aqueous solvent system, for example aqueous ethanol, and the reaction mixture is typically subjected to heating, for example to a temperature in excess of 100°C.

Many boronates suitable for use in preparing compounds of the invention are commercially available, for example from Boron Molecular Limited of Noble Park, Australia, or from Combi-Blocks Inc, of San Diego, USA. Where the boronates are not commercially available, they can be prepared by methods known in the art, for example as described in the review article by N. Miyaura and A. Suzuki, *Chem. Rev.* 1995, *95*, 2457. Thus, boronates can be prepared by reacting the corresponding bromo-compound with an alkyl lithium such as butyl lithium and then reacting with a borate ester. The resulting boronate ester derivative can, if desired, be hydrolysed to give the corresponding boronic acid.

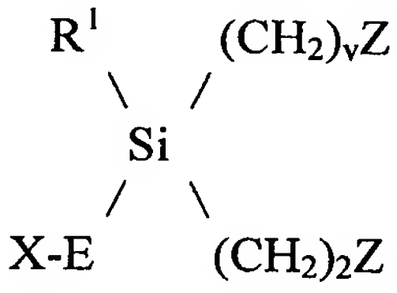
Compounds of formula (Xa):



(Xa)

where R^1, R^3, X and E are as defined above and v is 2 or 3;

may be prepared by reacting a compound of general formula (XII):



(XII)

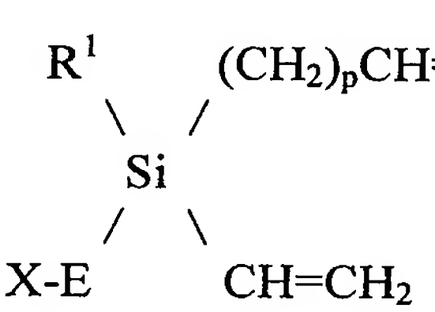
wherein R^1, R^3, X, E and v are as defined above and Z is halogen, especially Br;

with a compound of formula (XIII):

$$NHR^3 \qquad \text{(XIII)}$$

The reaction may be carried out in an organic solvent and at a temperature of from 40 to 100°C.

Compounds of formula (XII) may be prepared from compounds of general formula (XIV):



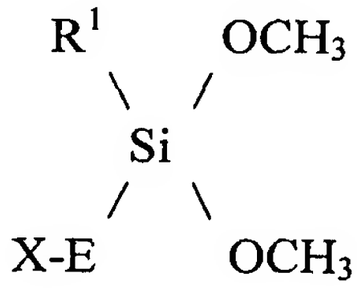
(XIV)

where R^1, R^3, X and E are as defined above and p is 0 or 1.

When p is 0, the compound of general formula (XIV) may be reacted with a hydrogen halide, especially hydrogen bromide. The reaction may be conducted by bubbling HBr gas through a solution of the compound of formula (XIV) in a non-polar organic solvent such as pentane and in the presence of radical initiator such as dibenzoyl peroxide to give a compound of formula (XII) in which v is 2.

When p is 1, the compound of general formula (XIV) may be treated by hydroboration under oxidising conditions (for example in the presence of hydrogen peroxide) to give a primary alcohol, followed by reaction with triphenyl phosphine and a carbon tetrahalide, especially carbon tetrabromide to give the compound of formula (XII) in which v is 3.

Compounds of formula (XIV) may be prepared from compounds of general formula (XV):



(XV)

where R^1, E and X are as defined above;

by reaction with Grignard reagents of formula (XVI)

$$CH_2=CH-(CH_2)_pMg-Z \qquad (XVI)$$

where p is 0 or 1 and Z is a halogen, especially Cl or Br.

For compounds of formula (XIV) in which p is 0, the compound of formula (XV) may be reacted with a single Grignard reagent of formula (XVI). However, for compounds of formula (XIV) where p is 1, two sequential reactions may be carried out using a compound of formula (XVI) in which p is 1 followed by a compound of formula (XVI) in which p is 0.

Compounds of formula (XV) may be prepared by the reaction of Grignard reagents of general formula (XVII):

$$R^1-Mg-Z \qquad (XVII)$$

where R^1 is as defined above and Z is halogen, but especially Cl or Br;

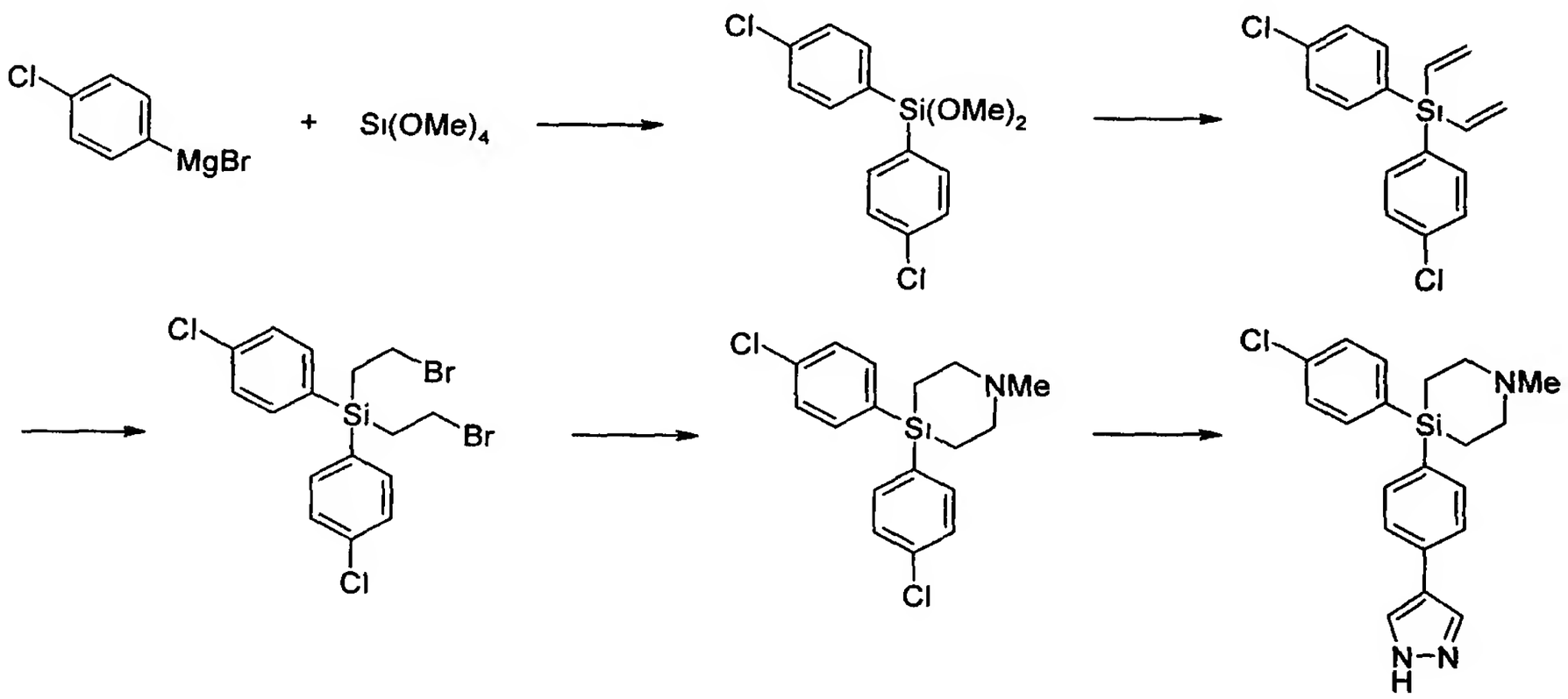
and (XVIII):

X-E-Mg-Z (XVIII)

where E and X are as defined above and Z is halogen, but especially Cl or Br;

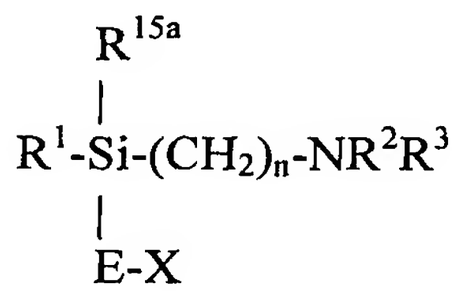
with tetramethoxysilane. The reaction is carried out in an inert atmosphere such as nitrogen and in an organic solvent such as diethyl ether.

Scheme 1 below shows the route to an example compound of the type described above.



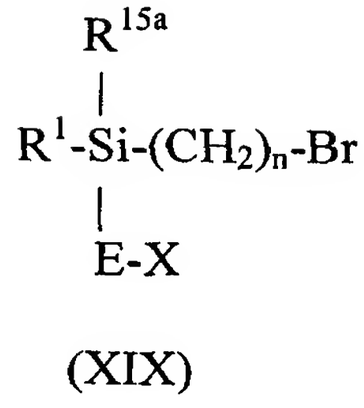
Scheme 1

Compounds of formula (Xb):



(Xb)

where X, E R^2, R^3 are as defined above, R^{15a} is C_1-C_4 alkyl and n is 2 or 3; may be prepared from compounds of general formula (XIX):



(XIX)

where R^1, R^{15a}, X, E and n are as defined above;

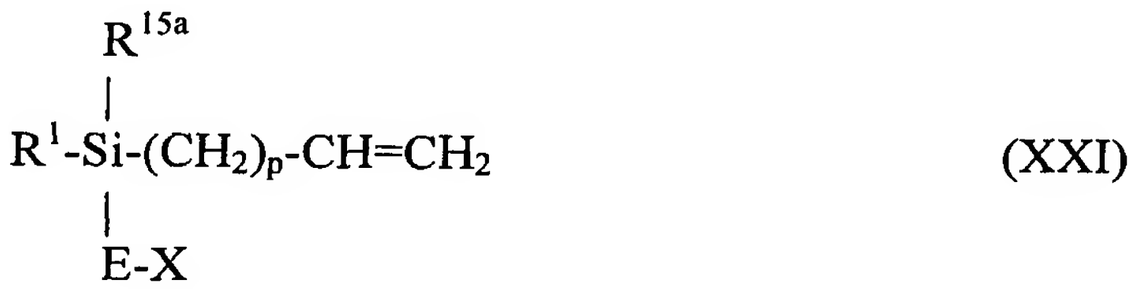
by reaction with a compound of formula (XX):

NHR^2R^3 (XX)

where R^2 and R^3 are as defined above.

The reaction may be conducted at raised temperature, for example about 40 to 80°C.

Compounds of formula (XIX) may be prepared from alkene derivatives of formula (XXI):



(XXI)

where R^1, R^{15a}, X and E are as defined above and p is 0 or 1;

When p is 0, the compound of general formula (XXI) may be reacted with a hydrogen halide, especially hydrogen bromide. The reaction may be conducted by bubbling HBr gas through a solution of the compound of formula (XXI) in a non-polar organic solvent such as pentane and in the presence of radical initiator such as dibenzoyl peroxide to give a compound of formula (XIX) in which n is 2.

When p is 1, the compound of general formula (XXI) may be treated by hydroboration under oxidising conditions (for example in the presence of hydrogen peroxide) to give a primary alcohol, followed by reaction with triphenyl phosphine and a carbon tetrahalide, especially carbon tetrabromide to give the compound of formula (XIX) in which n is 3.

Compounds of formula (XXI) may be prepared by reacting a compound of formula (XV) as defined above sequentially with Grignard reagents of formulae (XVI) as defined above and (XXII):

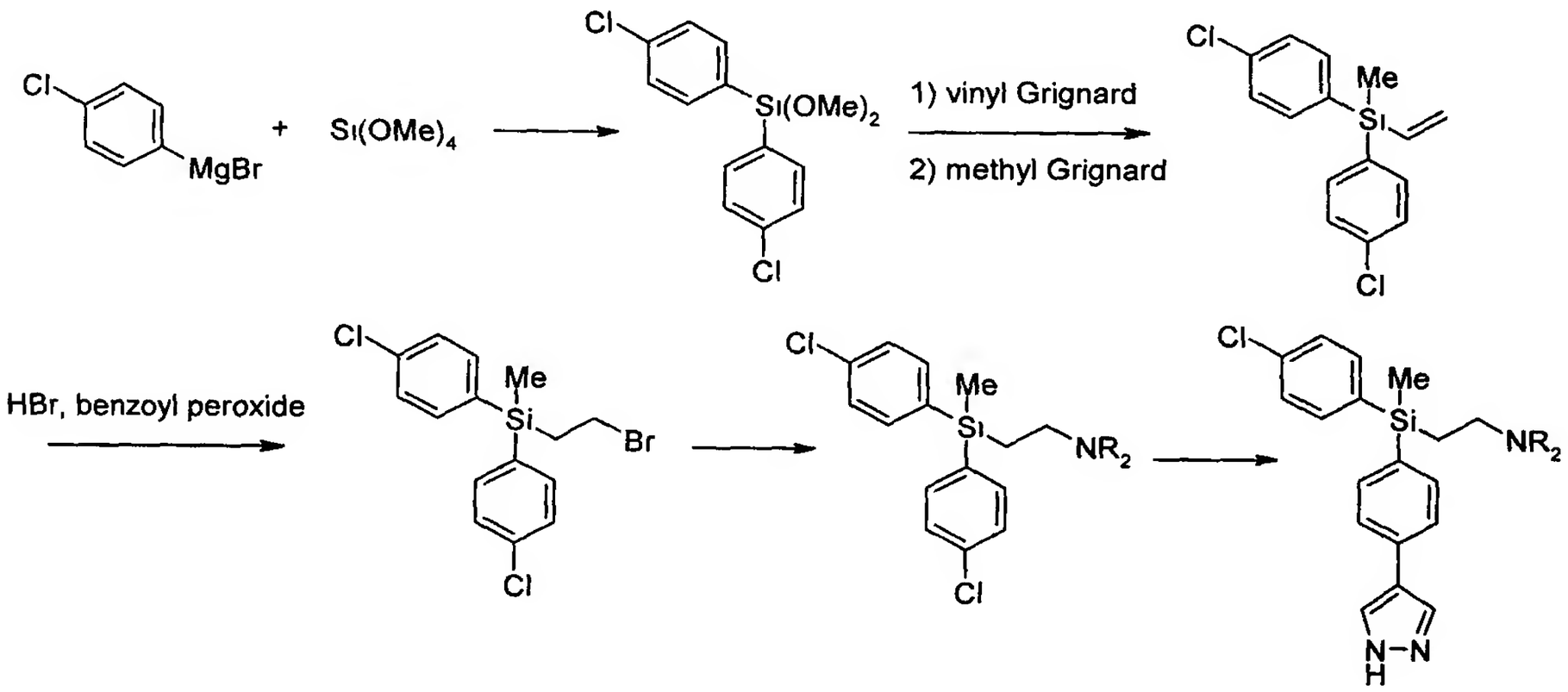
$$R^{15a}\text{-Mg-}Z \qquad \text{(XXII)}$$

where Z is a halogen, especially Cl or Br.

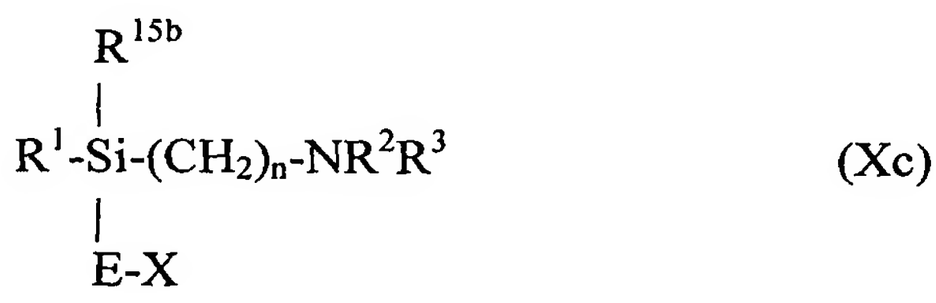
The reactions may be carried out under an inert atmosphere such as nitrogen and in an organic solvent such as diethyl ether.

Scheme 2 shows the route to an example compound of the type described above.

SCHEME 2



Compounds of formula (Xc):



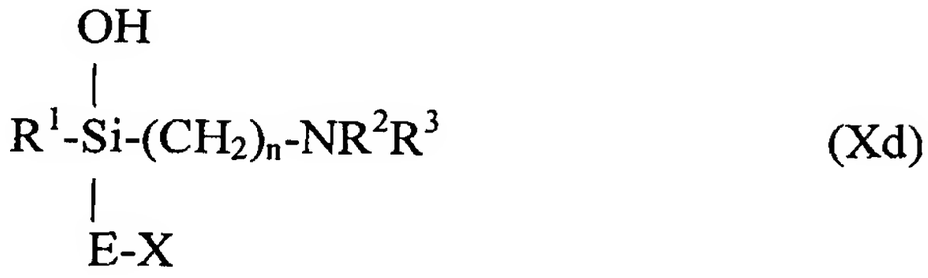
$$R^{1}\text{-}Si(R^{15b})(E\text{-}X)\text{-}(CH_2)_n\text{-}NR^2R^3 \qquad \text{(Xc)}$$

where X, E, R^1, R^2, R^3 are as defined above;

R^{15b} is C_1-C_4 alkoxy, optionally substituted by one or more halogen atoms or phenoxy optionally substituted by one or more halogen or C_1-C_4 alkyl groups; and

n is 2 or 3;

may be prepared from compounds of formula (Xd):



(Xd)

where X, E, R^1, R^2, R^3 are as defined above.

Compounds of formula (Xc) in which R^{15b} is a phenoxy or substituted phenoxy group may be prepared using a Mitsunobu reaction in which the compound of formula (Xd) is reacted with phenol or a substituted phenol of formula (XXIII) in the presence of triphenyl phosphine and diisopropyl azodicarboxylate.

R^{15b}-H (XXIII)

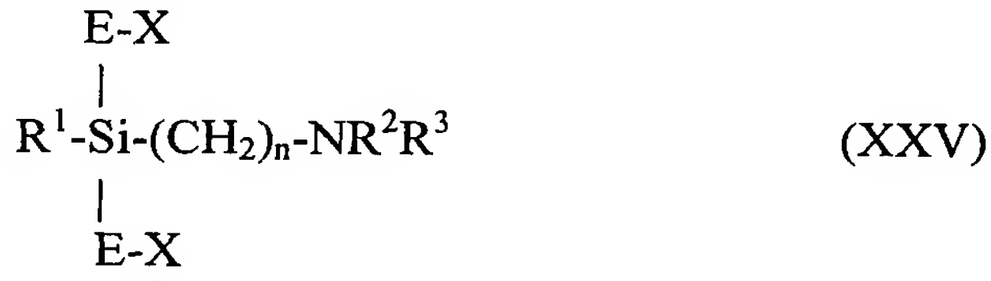
wherein R^{15b} is as defined above.

Compounds of formula (Xc) in which R^{15b} is an alkoxy or substituted alkoxy group may be prepared by reacting the compound of formula (Xd) with an alkylating agent, for example a diazo compound of formula (XXIV):

$R^{25}=N_2$ (XXIV)

where R^{25} is a C_1-C_4 alkenylene group corresponding to the required R^{15b} group. Thus, for example, when the required R^{15b} group is methoxy, R^{25} is CH_2.

Compounds of formula (Xd) may be prepared from compounds of formula (XXV):

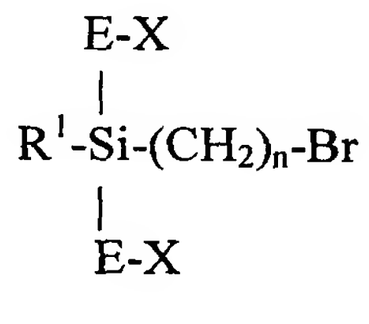


(XXV)

where X, E, R^2, R^3 are as defined above;

by reaction with trifluoromethylsulfonic acid followed by aqueous sodium hydroxide. This type of reaction is described in GB-A-2383575.

Compounds of formula (XXV) may be prepared by reacting a compound of formula (XXVI):



(XXVI)

where R^1, R^{15a}, X, E and n are as defined above;

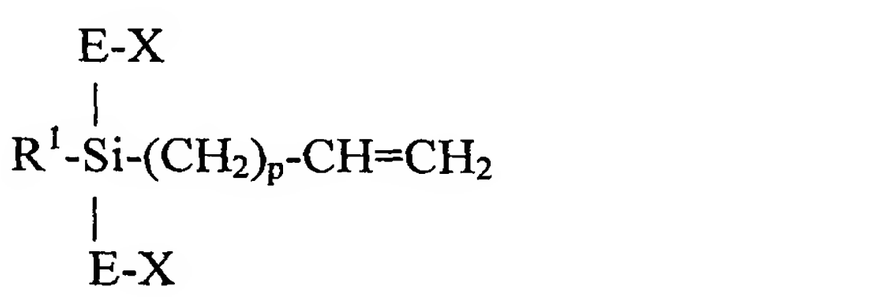
by reaction with a compound of formula (XX) as defined above:

(XX)

where R^2 and R^3 are as defined above.

The reaction may be conducted at raised temperature, for example about 40 to 80°C.

Compounds of formula (XXVI) may be prepared from compounds of formula (XXVII):



(XXVII)

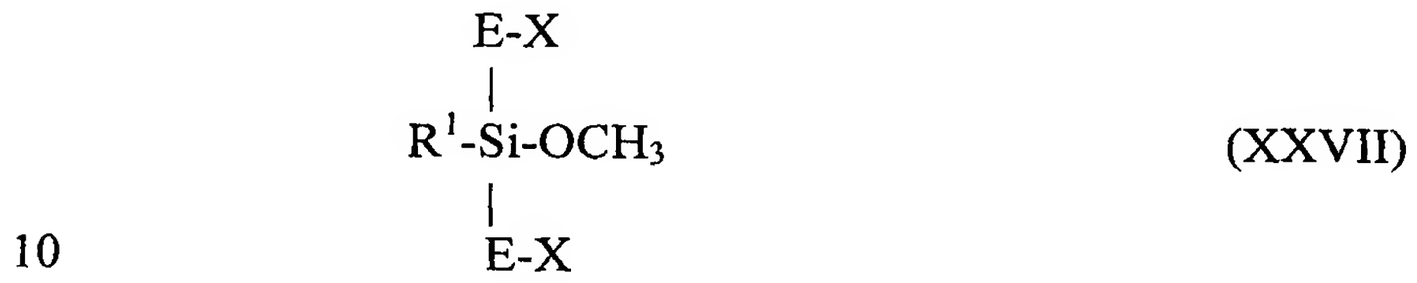
where R^1, X and E are as defined above and p is 0 or 1;

When p is 0, the compound of general formula (XXVII) may be reacted with a hydrogen halide, especially hydrogen bromide. The reaction may be conducted by bubbling HBr gas through a solution of the compound of formula (XXVII) in a non-polar organic solvent such as pentane and in the presence of radical initiator such as dibenzoyl peroxide to give a compound of formula (XXVI) in which n is 2.

When p is 1, the compound of general formula (XXVII) may be treated by hydroboration under oxidising conditions (for example in the presence of hydrogen

peroxide) to give a primary alcohol, followed by reaction with triphenyl phosphine and a carbon tetrahalide, especially carbon tetrabromide to give the compound of formula (XXVI) in which n is 3.

Compounds of formula (XXVII) may be prepared from compounds of formula (XXVIII):



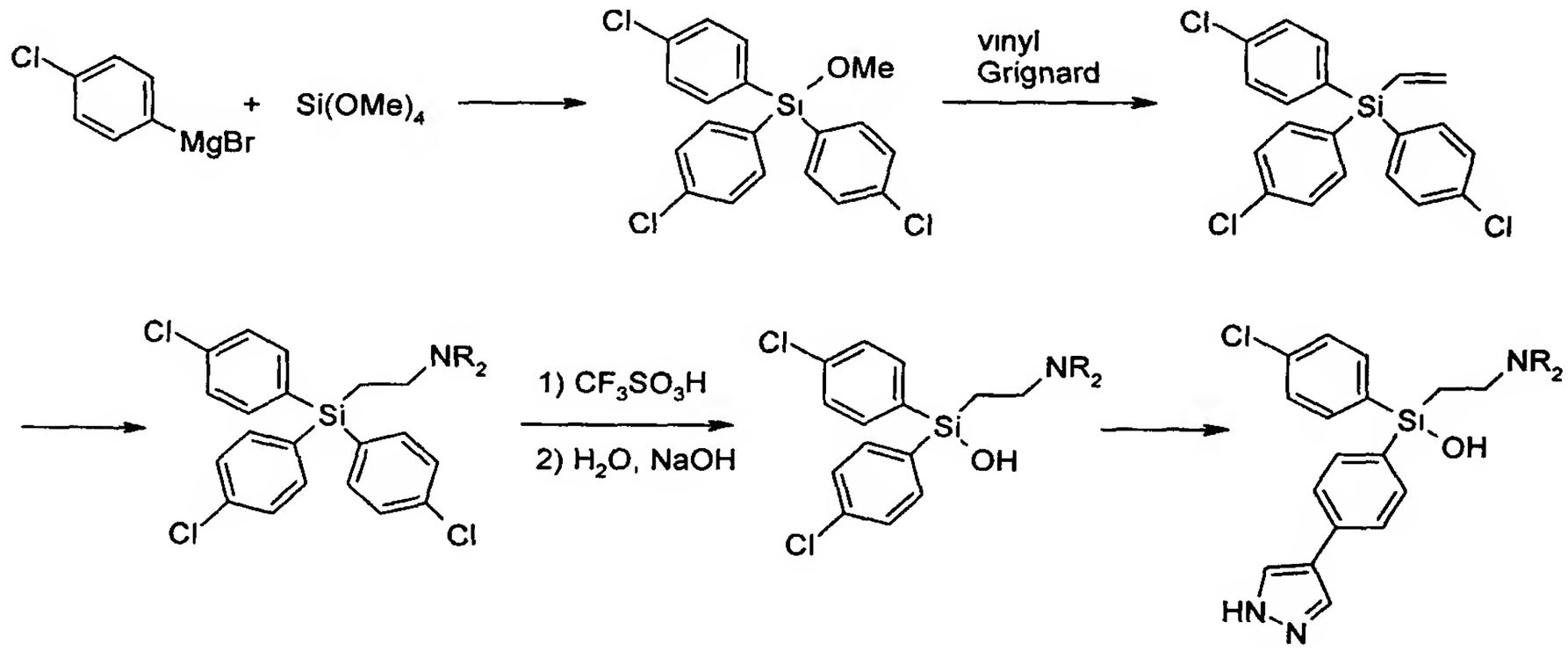
(XXVII)

where R^1, X and E are as defined above and p is 0 or 1;
by reaction with a Grignard reagent of formula (XVI) as defined above.

Compounds of formula (XXVII) may be prepared from tetramethoxysilane by reaction sequentially with one equivalent of a Grignard reagent of formula (XVII) and two equivalents of a Grignard reagent of formula (XVIII) as defined above.

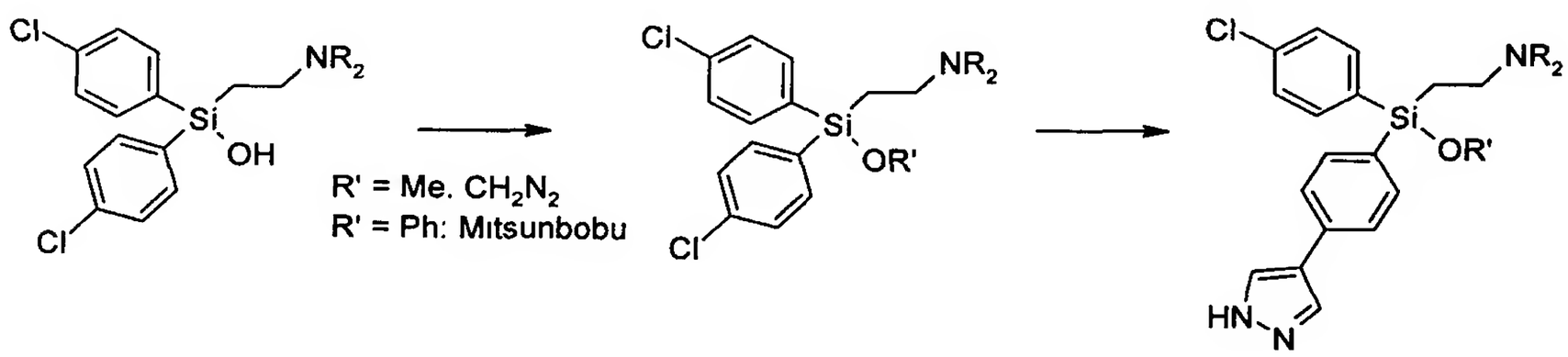
Scheme 3 shows a method for the synthesis of a compound of formula (Xd) and its conversion to a compound of formula (I)

SCHEME 3

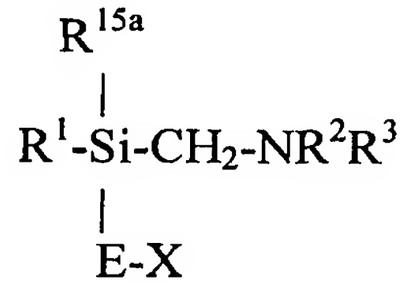


Scheme 4 shows the synthesis of compounds of formula (Xc) in which R^{15b} is phenoxy or methyl from corresponding compounds of formula (Xd) and their conversion to compound of formula (I).

SCHEME 4

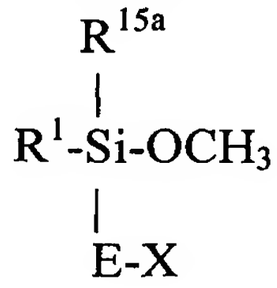


Compounds of formula (Xe)



(Xe)

where R^1, R^2, R^3, R^{15a}, E and X are as described above may be prepared from compounds of formula (XXVIII):



(XXVIII)

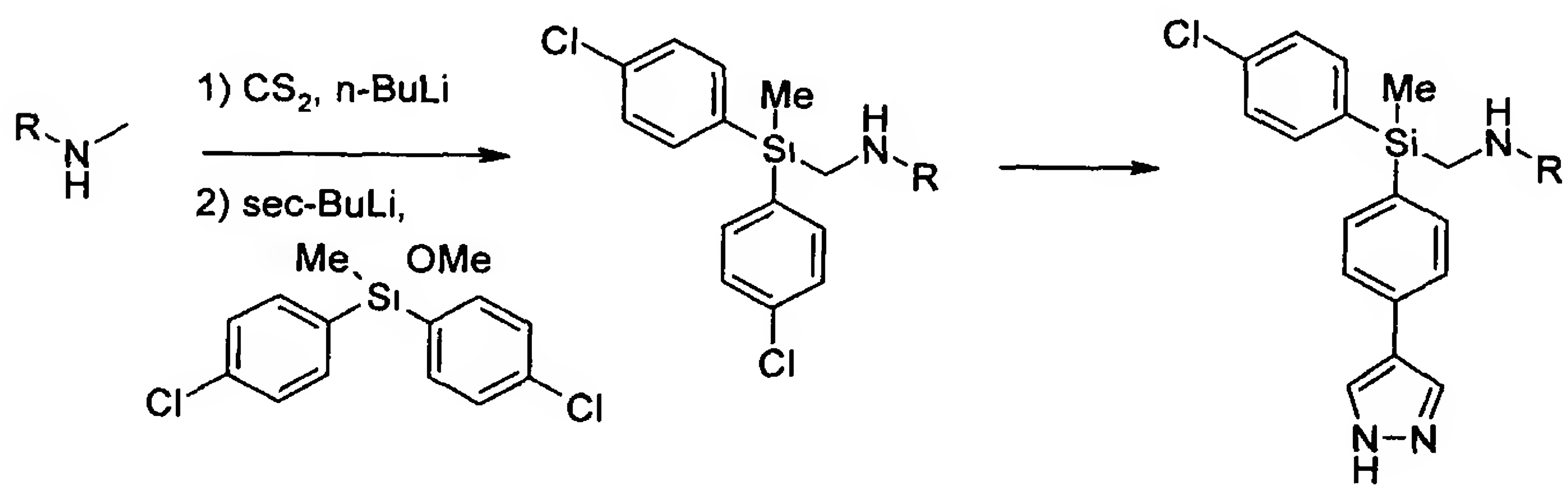
where R^1, R^{15a}, E and X are as defined above;

by reaction with a compound of formula (XX) as defined above. In the first step of the reaction, the compound of formula (XX) is treated with carbon disulfide and n-butyl lithium as described in *Synthesis*, **8**, 637-640 (1991). Following this, sec-butyl lithium and the compound of formula (XXVIII) are added to the reaction mixture.

Compounds of formula (XXVIII) may be prepared from compounds of formula (XV) as defined above by reaction with a Grignard reagent of formula (XXII).

An example of the preparation of a compound of formula (Xe) and its conversion to a compound of formula (I) is shown in Scheme 5.

SCHEME 5



Compounds of formula (Xf):

$$\underset{\substack{|\\ \text{E-X}}}{R^1}\text{-}(CR^{16}R^{17})_x\text{-}Si(R^{15})_2\text{-}(CR^{16}R^{17})_y\text{-}NR^2R^3 \qquad \text{(Xf)}$$

where R^1, R^2, R^3, R^{15}, E and X are as defined above, R^{16} and R^{17} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, OH, or F or R^{16} and R^{17} may combine to form a C=O; wherein the alkyl and alkoxy groups may be substituted with OH, oxo or F

provided that the carbon atom adjacent the NR^2R^3 moiety does not have a fluoro or oxo substituent;

and x and y are each 1 or 2, provided that x and y cannot both be 2;

may be prepared by reacting a compound of formula (XXX):

$$\underset{\substack{|\\ \text{E-X}}}{R^1}\text{-}(CR^{16}R^{17})_x\text{-}Si(R^{15})_2\text{-}OCH_3 \qquad \text{(XXX)}$$

wherein R^1, R^{15}, R^{16}, R^{17}, E, X and x are as defined above;
with a compound of formula (XXXI):

$$Li\text{-}(CR^{16}R^{17})_y\text{-}NR^2R^3 \qquad \text{(XXXI)}$$

wherein R^2, R^3, R^{16}, R^{17} and y are as defined above.
In the first step of the reaction, the compound of formula (XXXI) is treated with carbon disulfide and n-butyl lithium as described in *Synthesis*, **8**, 637-640 (1991). Following this, sec-butyl lithium and the compound of formula (XXX) are added to the reaction mixture.

Compounds of formula (XXX) may be prepared from compounds of formula (XXXII):

$$R^1\text{-}(CR^{16}R^{17})_x\text{-}\underset{\displaystyle E\text{-}X}{\overset{\displaystyle |}{Si}}\text{-}O(CH_3)_3 \qquad \text{(XXXII)}$$

wherein R^1, R^{16}, R^{17}, E, X and x are as defined above;

by reaction with two equivalents of a Grignard reagent of formula (XXXIII):

$$R^{15}\text{-}Mg\text{-}Z \qquad \text{(XXXIII)}$$

where R^{15} is as defined above and Z is halogen, preferably Cl or Br.

Compounds of formula (XXXII) may be prepared from compounds of formula (XXXIV):

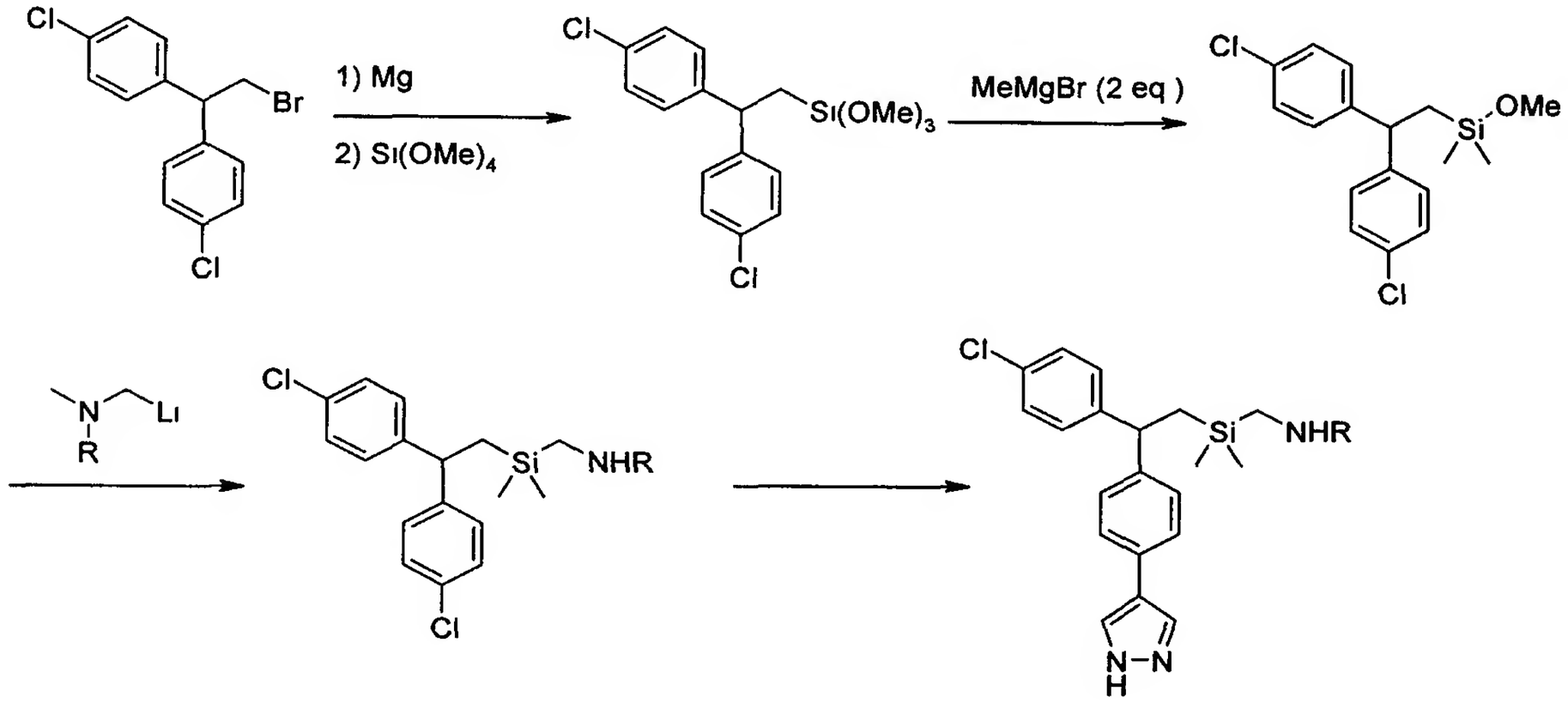
$$R^1\text{-}(CR^{16}R^{17})_x\text{-}\underset{\displaystyle E\text{-}X}{\overset{\displaystyle |}{Br}} \qquad \text{(XXXIV)}$$

wherein R^1, R^{16}, R^{17}, E, X and x are as defined above;

by reaction with magnesium followed by tetramethoxysilane.

This route to compounds of formula (Xf) and their subsequent converstion to compounds of formula (I) is shown in Scheme 6.

SCHEME 6



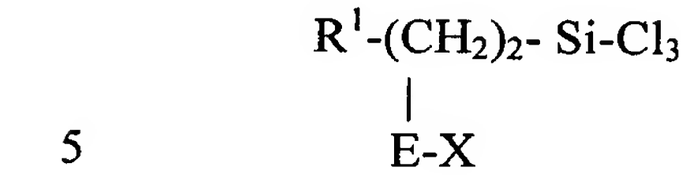
An alternative method for the preparation of a compound of formula (Xf) in which R^{16} and R^{17} are hydrogen, x is 2 and y is 1 is by the reaction of a compound of formula (XXXV):

(XXXV)

wherein R^1, R^{15}, E and X are as defined above;

with a compound of formula (XXXI) as defined above. The reaction may be carried out using the same conditions described for the preparation of the compound of formula (Xf) from the compound of formula (XXX).

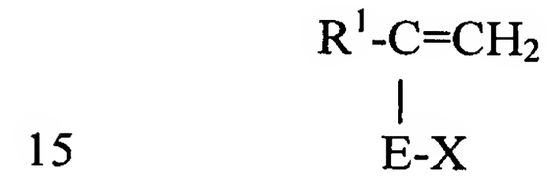
Compounds of formula (XXXV) may be prepared from compounds of formula (XXXVI):



(XXXVI)

wherein R^1, E and X are as defined above;
by reaction with two equivalents of a Grignard reagent of formula (XXXIII) as defined above.

Compounds of formula (XXXVI) may be prepared from compounds of formula (XXXVII):

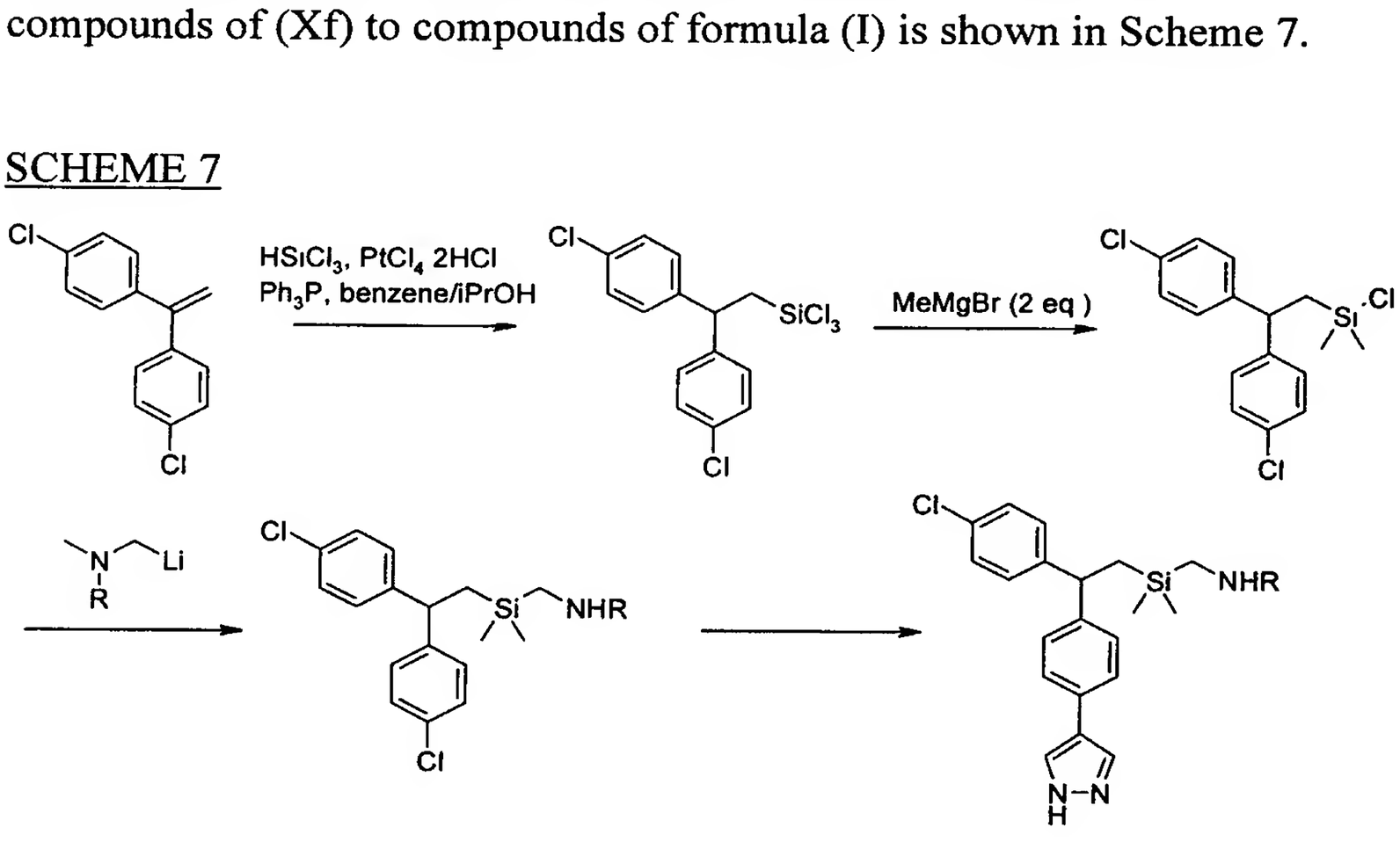


(XXXVII)

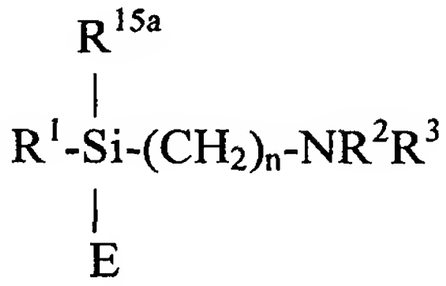
where R^1, E and X are as defined above;
by reaction with $HSiCl_3$ in the presence of a $PtCl_4$ catalyst and triphenylphosphine in a benzene/isopropylalcohol solvent as described by Ojima *et al*, *Organomet. Chem.* (1976), 111, 43.

This alternative route to compounds of formula (Xf) and the conversion of compounds of (Xf) to compounds of formula (I) is shown in Scheme 7.

SCHEME 7



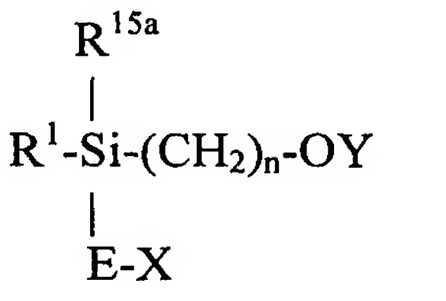
Compounds of formula (I) in which A is:



(where R^1, E and NR^2R^3 are not part of the group A but are included to show the position of the group A within the compound of formula (I));

and n is 2 or 3

may alternatively be prepared from compounds of formula (XL):



(XL)

where R^1, R^{15a}, E, X are as defined above, n is 2 or 3, and Y is a leaving group such as toluene sulfonyl or methane sulfonyl;

by reacting with a compound of formula (XI) as defined above, followed by reaction of the protected product compound with a compound of formula (XX) as defined above to introduce the NR^2R^3 group.

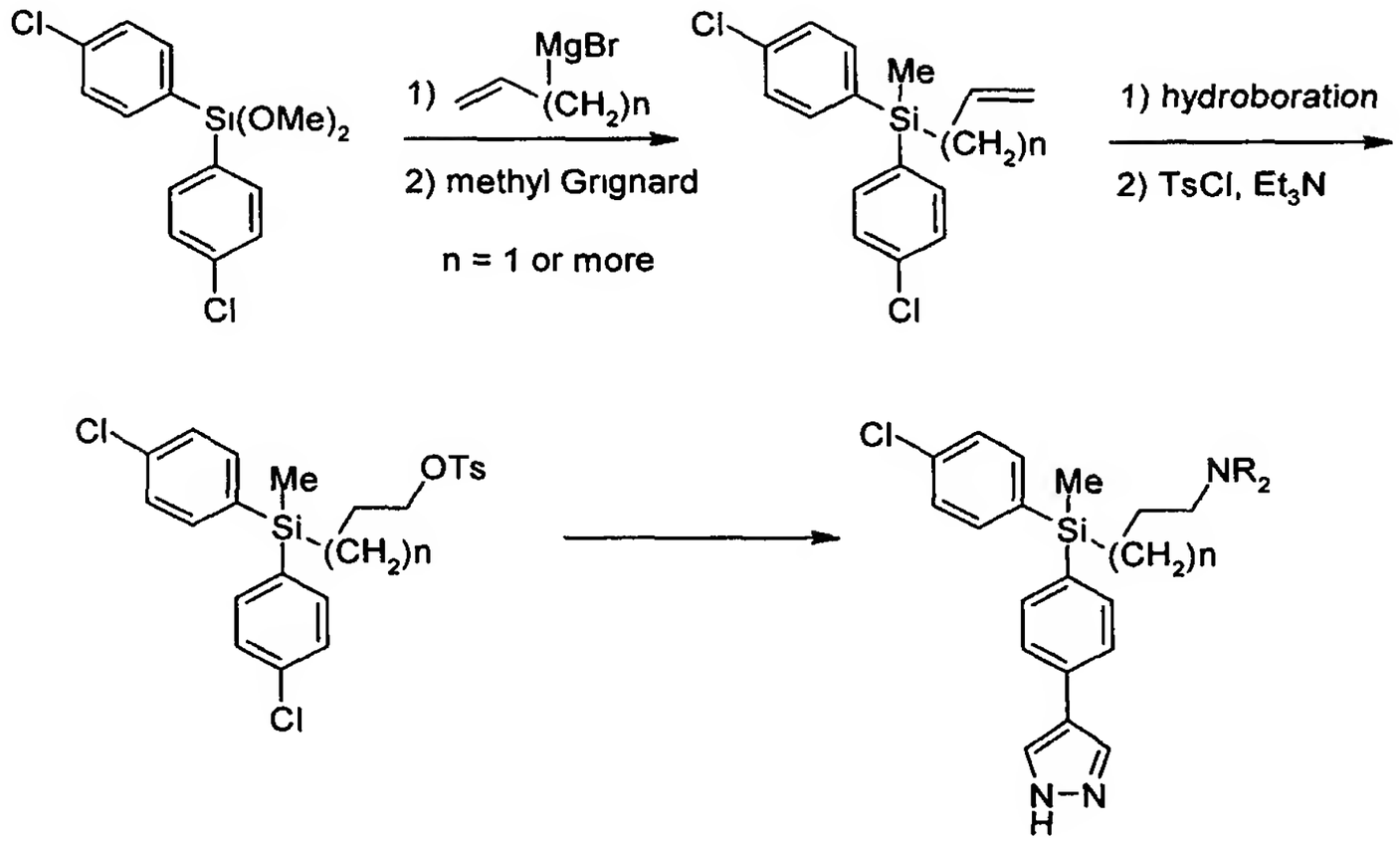
The compound of formula (XL) may be prepared from a compound of formula (XXI) as defined above by hydroboration followed by reaction with a compound of formula (XLI):

(XLI)

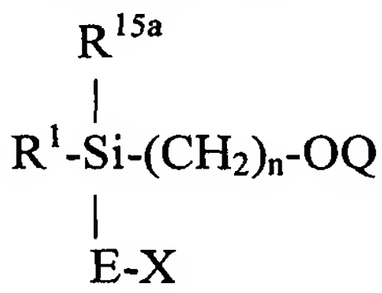
where Y is defined above;
in the presence of a base such as triethylamine.

This route is summarised in Scheme 8 below.

SCHEME 8



Alternatively, a compound of formula (XL) can be prepared by deprotecting a compound of formula (XLII):



(XLII)

where R^1, R^{15a}, E, X and n are as defined above, and Q is a suitable protecting group for an alcohol

followed by reaction with a compound of formula (XLI) as defined above in the presence of a base such as triethylamine.

Compounds of formula (XLXII) can be prepared from compounds of formula (XV) as defined above by reaction with a Grignard reagent of formula (XLII), which incorporates a protected alcohol.

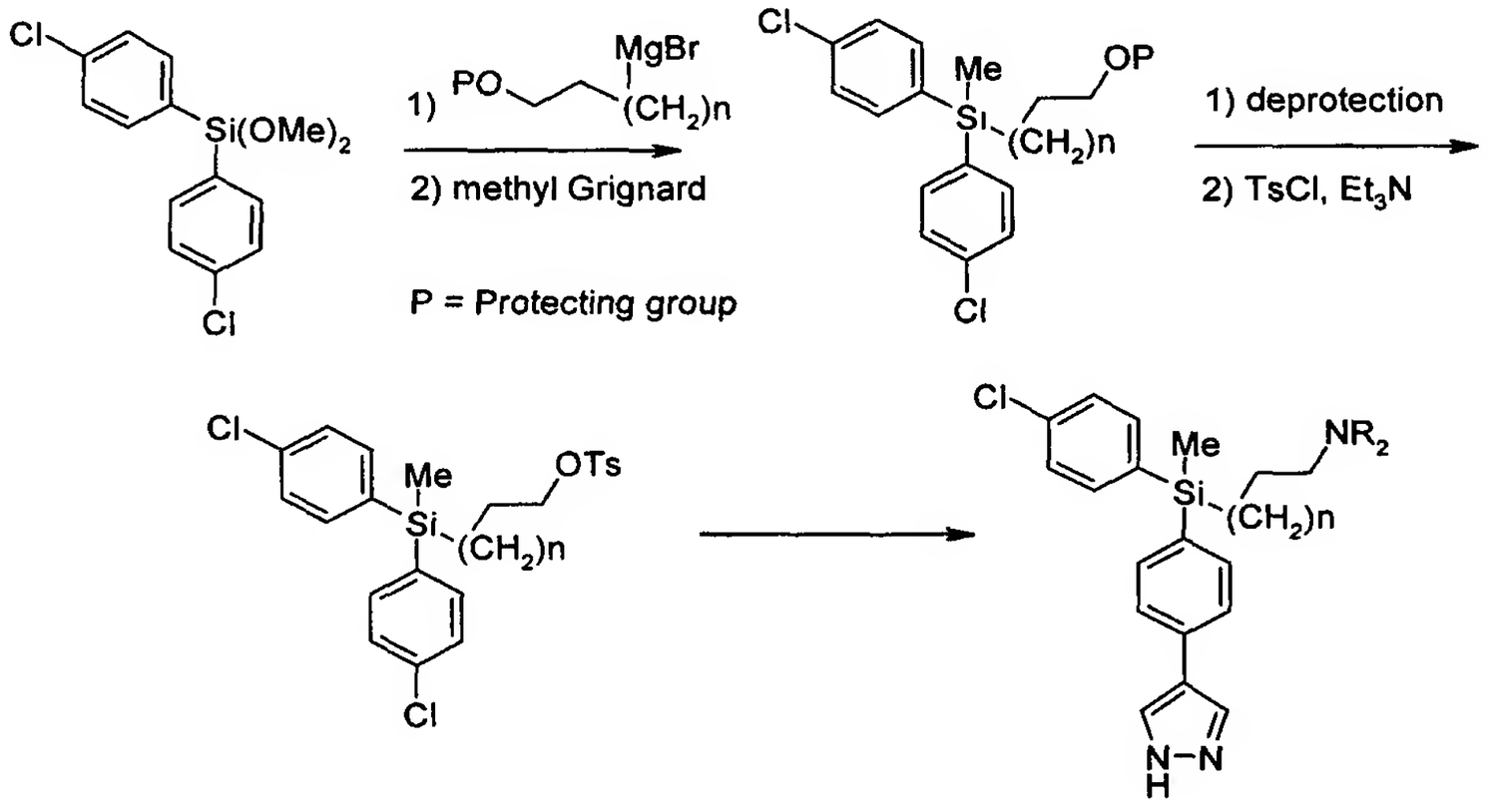
(XLII)

where p is 0 or 1 and Z is a halogen, especially Cl or Br and Q is a protecting group suitable for protecting an alcohol;

followed by reaction with a Grignard reagent of formula (XXII) as defined above.

This route is illustrated in Scheme 9.

SCHEME 9



Once formed, many compounds of the formula (I) can be converted into other compounds of the formula (I) using standard functional group interconversions. For example, compounds of the formula (I) in which the NR^2R^3 forms part of a nitrile group can be reduced to the corresponding amine. Compounds in which NR^2R^3 is an NH_2 group can be converted to the corresponding alkylamine by reductive alkylation, or to a cyclic group. Compounds wherein R^1 contains a halogen atom such as chlorine or bromine can be used to introduce an aryl or heteroaryl group substituent into the R^1 group by means of a Suzuki coupling reaction. Further examples of interconversions of one compound of the formula (I) to another compound of the formula (I) can be found in the examples below. Additional examples of functional group interconversions and reagents and conditions for carrying out such conversions can be found in, for example, *Advanced Organic Chemistry*, by Jerry March, 4th edition, 119, Wiley Interscience,

New York, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8).

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2-(phenylsulphonyl)ethyloxy amide (-NH-Psec). Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulphonyl (tosyl) and methanesulphonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl

ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

The 1(H) position of the pyrazole group in the compounds of the formula (I) or its precursors can be protected by a variety of groups, the protecting group being selected according to the nature of the reaction conditions to which the group is exposed. Examples of protecting groups for the pyrazole N-H include tetrahydropyranyl, benzyl and 4-methoxybenzyl groups.

Many of the chemical intermediates described above are novel and such novel intermediates form a further aspect of the invention.

Pharmaceutical Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier,

excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Accordingly, in a further aspect, the invention provides compounds of the formula (I) and sub-groups thereof as defined herein in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

In one preferred embodiment of the invention, the pharmaceutical composition is in a form suitable for i.v. administration, for example by injection or infusion.

In another preferred embodiment, the pharmaceutical composition is in a form suitable for sub-cutaneous (s.c.) administration.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, e.g. lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (e.g. tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 1 nanogram to 2 milligrams, for example 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams, or 0.1 milligrams to 2 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Protein Kinase Inhibitory Activity

The activity of the compounds of the invention as inhibitors of protein kinase A and protein kinase B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC50 value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 μM, more preferably less than 0.1 μM, against protein kinase B.

Therapeutic Uses

Prevention or Treatment of Proliferative Disorders

The compounds of the formula (I) are inhibitors of protein kinase A and protein kinase B. As such, they are expected to be useful in providing a means of preventing the growth of or inducing apoptosis of neoplasias. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with deletions or inactivating mutations in PTEN or loss of PTEN expression or rearrangements in the (T-cell lytmphocyte) TCL-1 gene may be particularly sensitive to PKB inhibitors. Tumours which have other abnormalities leading to an upregulated PKB pathway signal may also be particularly sensitive to inhibitors of PKB. Examples of such abnormalities include but are not limited to overexpression of one or more

PI3K subunits, over-expression of one or more PKB isoforms, or mutations in PI3K, PDK1, or PKB which lead to an increase in the basal activity of the enzyme in question, or upregulation or overexpression or mutational activation of a growth factor receptor such as a growth factor selected from the epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet derived growth factor receptor (PDGFR), insulin-like growth factor 1 receptor (IGF-1R) and vascular endothelial growth factor receptor (VEGFR) families.

It is also envisaged that the compounds of the invention will be useful in treating other conditions which result from disorders in proliferation or survival such as viral infections, and neurodegenerative diseases for example. PKB plays an important role in maintaining the survival of immune cells during an immune response and therefore PKB inhibitors could be particularly beneficial in immune disorders including autoimmune conditions.

Therefore, PKB inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

PKB inhibitors may also be useful in diseases resulting from insulin resistance and insensitivity, and the disruption of glucose, energy and fat storage such as metabolic disease and obesity.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, endometrium, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukaemia, acute lymphocytic leukaemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukaemias, myelodysplastic syndrome, or

promyelocytic leukaemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

A further subset of cancers includes breast cancer, ovarian cancer, prostate cancer, endometrial cancer and glioma.

It is also possible that some protein kinase B inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine of an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

<u>Immune Disorders</u>

Immune disorders for which PKA and PKB inhibitors may be beneficial include but are not limited to autoimmune conditions and chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease.

<u>Other Therapeutic Uses</u>

PKB plays a role in apoptosis, proliferation, differentiation and therefore PKB inhibitors could also be useful in the treatment of the following diseases other than cancer and those associated with immune dysfunction; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by protein kinase A and/or protein kinase B. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile manner.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, typically 10 nanograms to 10 milligrams per kilogram of bodyweight, more typically 1 microgram to 10 milligrams although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents or treatments that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to:

- Topoisomerase I inhibitors
- Antimetabolites
- Tubulin targeting agents
- DNA binder and topoisomerase II inhibitors
- Alkylating Agents
- Monoclonal Antibodies.
- Anti-Hormones
- Signal Transduction Inhibitors
- Proteasome Inhibitors
- DNA methyl transferases

- Cytokines and retinoids
- Radiotherapy.

For the case of protein kinase A inhibitors or protein kinase B inhibitors combined with other therapies the two or more treatments may be given in individually varying dose schedules and via different routes.

Where the compound of the formula (I) is administered in combination therapy with one or more other therapeutic agents, the compounds can be administered simultaneously or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one, two, three, four or more other therapeutic agents can be, for example, formulated together in a dosage form containing two, three, four or more therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

A person skilled in the art would know through their common general knowledge the dosing regimes and combination therapies to use.

Methods of Diagnosis

Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be

suffering is one which would be susceptible to treatment with a compound having activity against protein kinase A and/or protein kinase B.

For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to up-regulation of PKA and/or PKB or to sensitisation of a pathway to normal PKA and/orPKB activity, or to upregulation of a signal transduction component upstream of PKA and/or PKB such as, in the case of PKB, P13K, GF receptor and PDK 1 & 2.

Alternatively, a biological sample taken from a patient may be analysed for loss of a negative regulator or suppressor of the PKB pathway such as PTEN. In the present context, the term "loss" embraces the deletion of a gene encoding the regulator or suppressor, the truncation of the gene (for example by mutation), the truncation of the transcribed product of the gene, or the inactivation of the transcribed product (e.g. by point mutation) or sequestration by another gene product.

The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of PKA and/or PKB. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of PKA and/or PKB. The term marker also includes markers which are characteristic of up regulation of PKA and/or PKB, including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

The above diagnostic tests and screens are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and

enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, or urine.

Identification of an individual carrying a mutation in PKA and/or PKB or a rearrangement of TCL-1or loss of PTEN expression may mean that the patient would be particularly suitable for treatment with a PKA and/or PKB inhibitor. Tumours may preferentially be screened for presence of a PKA and/or PKB variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody.

Methods of identification and analysis of mutations and up-regulation of proteins are known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridisation.

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc., or Innis, M.A. et-al., eds. PCR Protocols: a guide to methods and applications, 1990, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al., 2001, 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference.

An example of an in-situ hybridisation technique for assessing mRNA expression would be fluorescence in-situ hybridisation (FISH) (see Angerer, 1987 Meth. Enzymol., 152: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labeled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in Molecular Medicine.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of PKB, or detection of PKB variants could be applicable in the present case.

Therefore all of these techniques could also be used to identify tumours particularly suitable for treatment with PKA and/or PKB inhibitors.

For example, as stated above, PKB beta has been found to be upregulated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19,

2324 – 2330). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB beta, may be used to treat ovarian and pancreatic cancers.

PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB alpha, may be used to treat human gastric, prostate and breast cancer.

Increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532). Therefore it is envisaged that PKB inhibitors, and in particular inhibitors of PKB gamma, may be used to treat steroid independent breast and prostate cancers.

EXPERIMENTAL

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following procedures and examples.

The starting materials for each of the procedures described below are commercially available unless otherwise specified.

In the examples, the compounds prepared were characterised by liquid chromatography, mass spectroscopy and ^{1}H nuclear magnetic resonance spectroscopy using the systems and operating conditions set out below.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 instrument operating at 400.13MHz, in Me-d_3-OD at 27C, unless otherwise stated and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity where s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad). The residual protic solvent MeOH (δ_H = 3.31 ppm) was used as the internal reference.

For the mass spectra, where chlorine is present, the mass quoted for the compound is for ^{35}Cl.

In each of the examples, where the compounds are isolated or formed as the free base, they can be converted into a salt form such as an acetic acid or hydrochloric acid salt. Conversely, where the compounds are isolated or formed as a salt, the salt can be converted into the corresponding free base by methods well known to the skilled person, and then optionally converted to another salt.

Platform System

HPLC System: Waters 2795

Mass Spec Detector: Micromass Platform LC

PDA Detector: Waters 2996 PDA

MS conditions:

Capillary voltage:	3.4 kV (3.40 kV on ES negative)
Cone voltage:	25 V
Source Temperature:	120 °C
Scan Range:	100-80000 amu
Ionisation Mode:	ElectroSpray Positive & Negative

Analytical conditions:

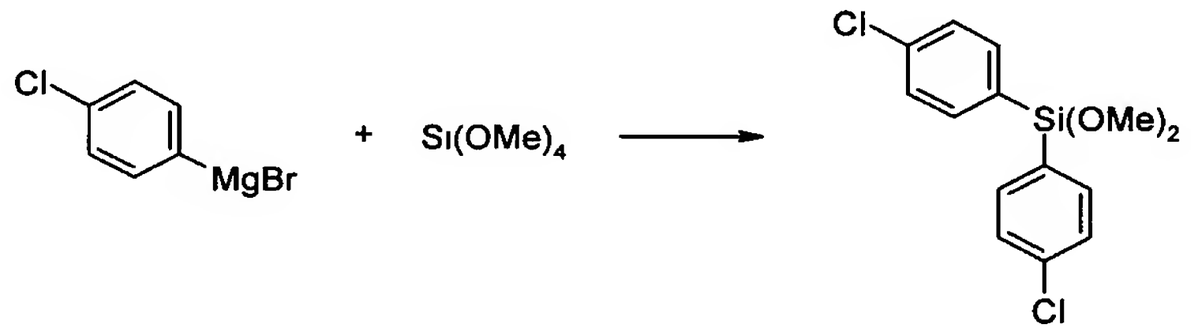
Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B over 15 minutes
Flow:	0.4 ml/min
Column:	Phenomenex Synergi 4µ MAX-RP 80A, 2.0 x 150mm

Analytical Lipophilic conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	55-95% eluent B over 3.5 minutes
Flow:	0.8 ml/min
Column:	Phenomenex Synergi 4µ MAX-RP 80A, 2.0 x 50mm

EXAMPLE 1 – Synthesis of 4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane and 1-methyl-4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane

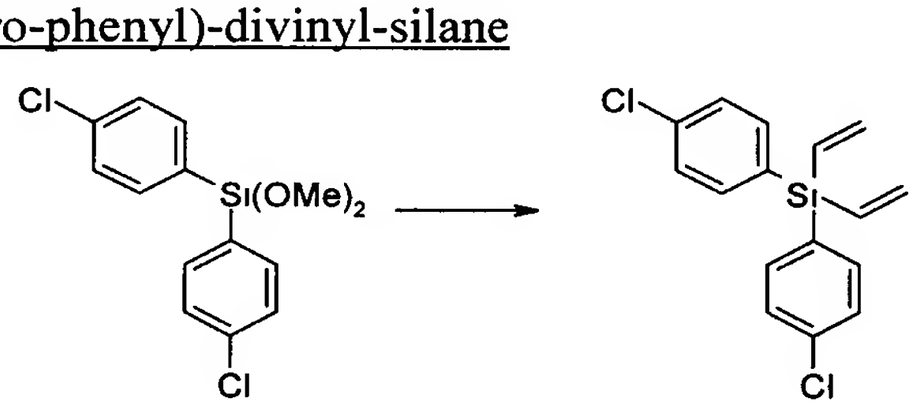
a. Bis-(4-chloro-phenyl)-dimethoxy-silane



Reference: GB023822575A

A solution of 4-chorophenylmagnesium bromide (1.0M in Et_2O, 34 mL, 34 mmol) was added to a solution of tetramethoxysilane (2.34 mL, 15.9 mmol) in Et_2O (20 mL) under nitrogen. The mixture was maintained at r.t. for 17 hours then heated to reflux for 3.5 hrs. After cooling to r.t., a precipitate was filtered off, this then being well washed with anhydrous ether. The filtrate was concentrated *in vacuo*, treated with pentane (50 mL) and filtered again, then concentrated a second time to give a greenish mobile oil (2.17 g, 80% pure by ^1H NMR). This was taken on to the following step without further purification. ^1H NMR ($CDCl_3$) δ 3.60 (6H, s), 7.37 (4H, d, J = 8.1 Hz), 7.55 (4H, d, J = 8.3 Hz).

b. Bis-(4-chloro-phenyl)-divinyl-silane

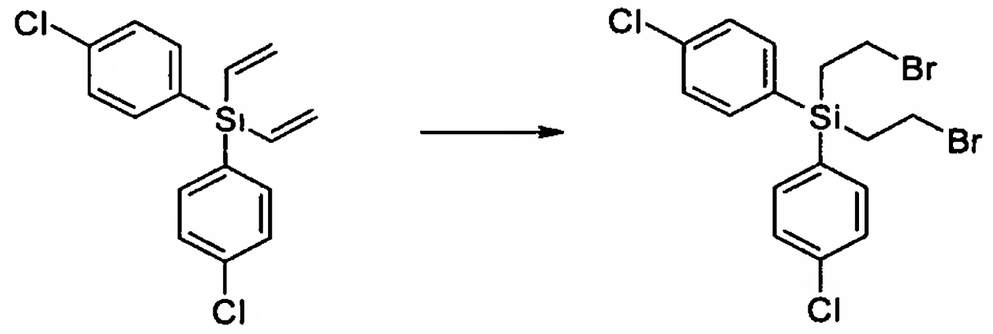


Reference: GB023822575A

A solution of vinylmagnesium chloride (1.6M in THF, 10 mL, 16 mmol) was added to a cold (-78 °C) solution of bis-(4-chloro-phenyl)-dimethoxy-silane (2.03g, 6.5 mmol) in Et_2O (20 mL) under nitrogen. The mixture was heated to reflux for 5.5 hrs then cooled in ice and quenched by the addition of saturated ammonium chloride

solution. The mixture was extracted with ethyl acetate/40-60 petrol (1:4), the organic phase then being washed with brine, dried ($MgSO_4$), filtered and concentrated to give a residue which was purified by flash chromatography (SiO_2), eluting with pentane to give the title compound as a colourless oil (1.02 g). ^1H NMR ($CDCl_3$) δ 5.79 (2H, dd, J = 20.0, 3.8 Hz), 6.28 (2H, dd, J = 14.7, 3.8 Hz), 6.43 (2H, dd, J = 20.0, 14.7 Hz), 7.35 (4H, d, J = 8.3 Hz), 7.43 (4H, d, J = 8.1 Hz).

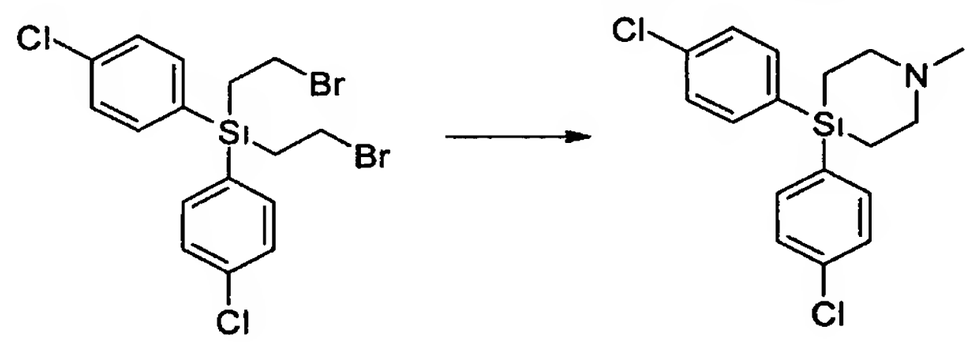
c. Bis-(2-bromo-ethyl)-bis-(4-chloro-phenyl)-silane



Reference: GB023822575A

HBr gas was bubbled through a solution of bis-(2-bromo-ethyl)-bis-(4-chloro-phenyl)-silane (722 mg, 2.36 mmol) and dibenzoyl peroxide (10 mg) in pentane (20 mL) for 14 hours. Approximately every 2 hours, further portions of dibenzoyl peroxide were added. The reaction mixture was poured onto ice and extracted with EtOAc/40-60 petrol (1:4). The organic phase was washed with sodium bicarbonate solution and brine then dried ($MgSO_4$), filtered and concentrated to give a residue which was purified by flash chromatography (SiO_2), eluting with 1% EtOAc/40-60 petrol to afford the title compound (805 mg). LCMS (lipophilic method) R_t 4.11 min. ^1H NMR ($CDCl_3$) δ 1.89-1.93 (4H, m), 3.42-3.64 (4H, m), 7.37-7.42 (8H, m).

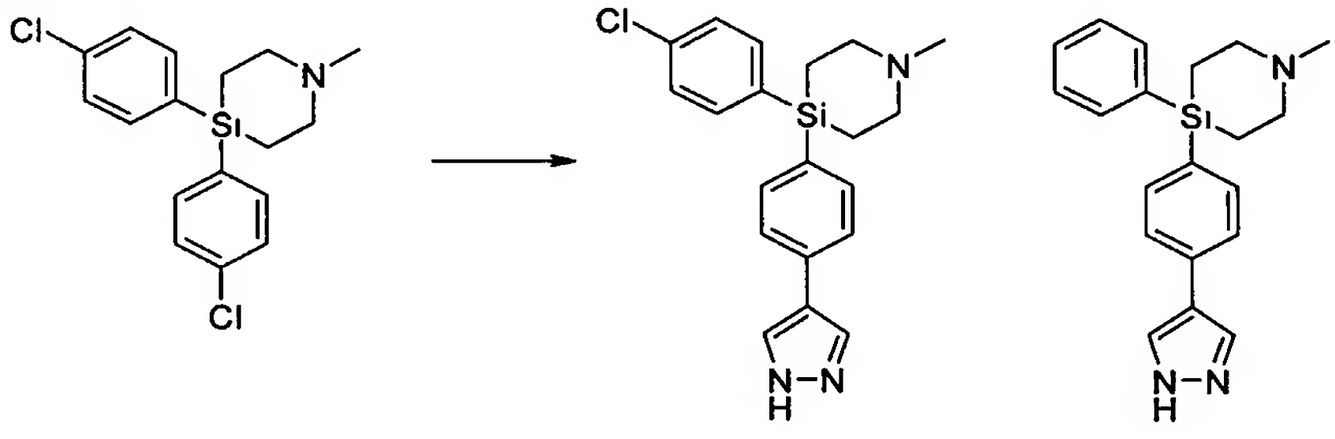
d. 4,4-Bis-(4-chloro-phenyl)-1-methyl-[1,4]azasilinane



A solution of methylamine in ethanol (8M, 0.1 mL, 0.8 mmol) was added to a solution of bis-(2-bromo-ethyl)-bis-(4-chloro-phenyl)-silane (198 mg, 0.42 mmol)

and triethylamine (0.24 mL, 1.6 mmol) in toluene (2 mL) and acetonitrile (2 mL). The mixture was heated at 70 °C in a sealed vessel for 6 hours, with additional portions of methylamine solution being added after 1 hour and 4 hours. After a further 16 hours at room temperature, the mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and 1N sodium hydroxide solution. The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated to give a residue which was purified by flash chromatography (SiO_2), eluting with methanol/DCM (gradient elution, 1%, 10%, 20%) to give the title compound (121 mg). LCMS (lipophilic method) R_t 1.64 min; *m/z* $[M+H]^+$ 336. ^1H NMR (methanol-d_4) δ 1.41 (4H, t, J = 6.3 Hz), 2.31 (3H, s), 2.76 (4H, t, J = 6.4 Hz), 7.40 (4H, d, J = 8.3 Hz), 7.52 (4H, d, J = 8.3 Hz).

e. 4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane and 1-methyl-4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane



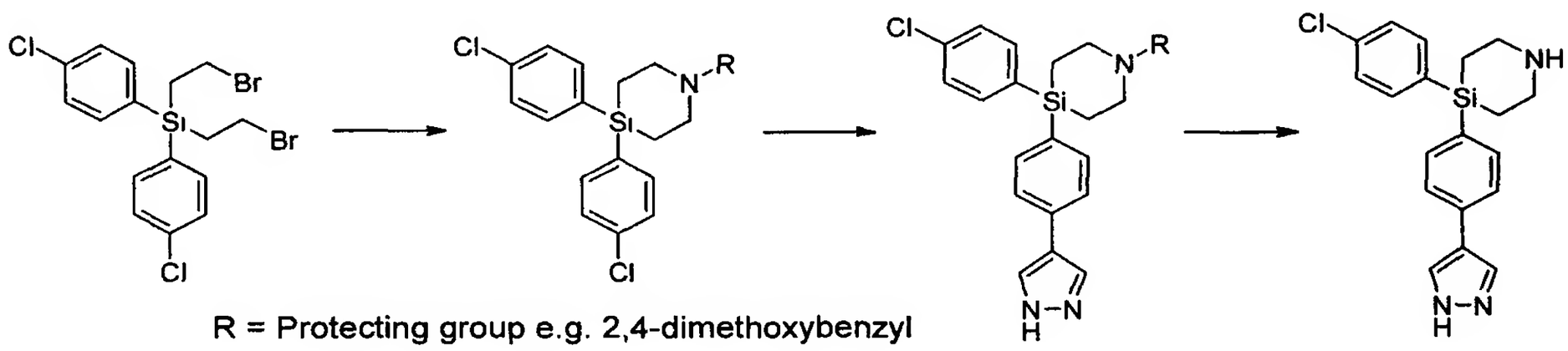
A mixture of 4,4-bis-(4-chloro-phenyl)-1-methyl-[1,4]azasilinane (121 mg, 0.36 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (70 mg, 0.36 mmol) and potassium phosphate (191 mg, 0.90 mmol) in toluene (1 mL)/methanol (1 mL)/ethanol (1 mL)/water (1 mL) was degassed with by purging with nitrogen. Bis(tri-*tert*-butylphosphine)palladium (0) (8 mg, 0.016 mmol) was added and degassing continued. The vial was sealed and the mixture heated at 135 °C for 30 minutes in a CEM Discover microwave. The mixture was partitioned between 1N sodium hydroxide solution and ethyl acetate The organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated to give a residue which was purified by flash chromatography (SiO_2), eluting with methanol/DCM (gradient elution, 1%,

2%, 5%) and then by preparative HPLC to give the title compounds: 4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane (3 mg as formate salt). LCMS (final compound method) R_t 6.62 min; *m/z* $[M+H]^+$ 368. ^1H NMR (methanol-d_4) δ 1.51-1.56 (4H, m), 2.54 (3H, s), 3.05-3.09 (4H, m), 7.42 (4H, d, *J* = 8.3 Hz), 7.55-7.58 (4H, m), 7.64 (4H, d, *J* = 8.1 Hz), 7.99 (2H, br.s), 8.56 (1H, br.s).

1-methyl-4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane (2 mg as formate salt). LCMS (final compound method) R_t 6.63 min; *m/z* $[M+H]^+$ 334. ^1H NMR (methanol-d_4) δ 1.58 (4H, t, *J* = 6.3 Hz), 2.62 (3H, s), 3.15-3.20 (4H, m), 7.40-7.45 (3H, m), 7.55-7.61 (4H, m), 7.64 (d, *J* = 7.8 Hz), 7.99 (2H, br.s), 8.55 (1H, br.s).

EXAMPLE 2 – Synthesis of 4-(4-Chloro-phenyl)- 4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane and 4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane

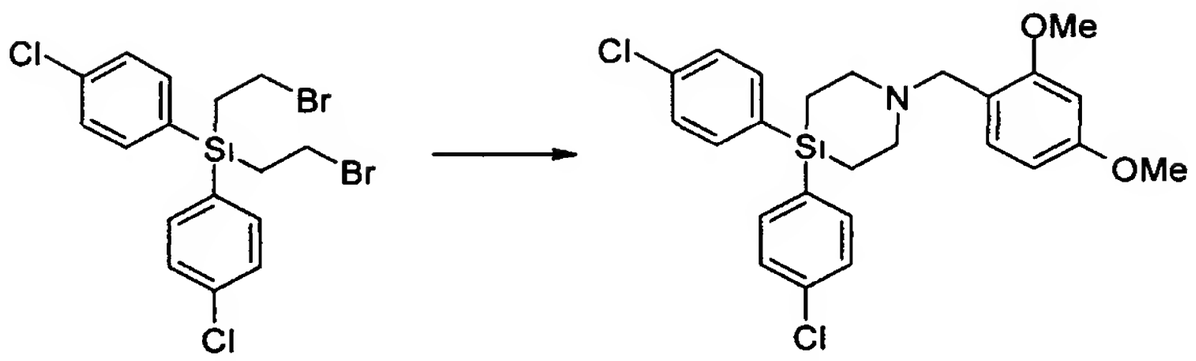
The proposed reaction scheme for the synthesis of these compounds is shown below.



R = Protecting group e.g. 2,4-dimethoxybenzyl

The first step of the synthesis has been carried out as follows:

a. 4,4-Bis-(4-chloro-phenyl)-1-(2,4-dimethoxy-benzyl)-[1,4]azasilinane



A solution of 2,4-dimethoxybenzylamine (71 mg, 0.42 mmol) in acetonitrile (4 mL) was added to a solution of bis-(2-bromo-ethyl)-bis-(4-chloro-phenyl)-silane (189 mg, 0.40 mmol) and triethylamine (0.14 mL, 1.0 mmol) in toluene (5 mL). The mixture was heated at 80 °C for 3 hours, then additional triethylamine (0.5 mL, 3.6 mmol) and heating maintained for a further 3 days. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and 50% saturated potassium carbonate solution. The aqueous phase was extracted a second time with ethyl acetate, then the organic phases were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to give a residue which was purified by filtration through silica, eluting with 1% triethylamine in ethyl acetate to give the title compound (155 mg, 80% pure by DAD). LCMS (lipophilic method) R_t 1.52 min; *m/z* $[M+H]^+$ 472. ^1H NMR (methanol-d_4) δ 1.36-1.41 (4H, m), 2.82-2.87 (4H, m), 3.59 (s, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 6.49 (1H, d, J = 8.1 Hz), 6.52 (1H, s), 7.19 (1H, d, J = 8.3 Hz), 7.39 (4H, d, J = 7.8 Hz), 7.51 (4H, d, J = 7.8 Hz).

The remainder of the synthesis will be carried out in a manner analagous to that of Example 1 above.

BIOLOGICAL ACTIVITY

EXAMPLE 3

Measurement of PKA Kinase Inhibitory Activity (IC_{50})

Compounds of the invention can be tested for PK inhibitory activity using the PKA catalytic domain from Upstate Biotechnology (#14-440) and the 9 residue PKA specific peptide (GRTGRRNSI), also from Upstate Biotechnology (#12-257), as the substrate. A final concentration of 1 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 40 μM ATP/γ^{33}P-ATP and 5 μM substrate. Compounds are

added in dimethylsulphoxide (DMSO) solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. Unincorporated γ^{33}P-ATP is then separated from phosphorylated proteins on a Millipore MAPH filter plate. The plates are washed, scintillant is added and the plates are then subjected to counting on a Packard Topcount.

The % inhibition of the PKA activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

EXAMPLE 4

Measurement of PKB Kinase Inhibitory Activity (IC_{50})

The inhibition of protein kinase B (PKB) activity by compounds can be determined determined essentially as described by Andjelkovic *et al.* (Mol. Cell. Biol. 19, 5061-5072 (1999)) but using a fusion protein described as PKB-PIF and described in full by Yang et al (Nature Structural Biology 9, 940 – 944 (2002)). The protein is purified and activated with PDK1 as described by Yang *et al.* The peptide AKTide-2T (H-A-R-K-R-E-R-T-Y-S-F-G-H-H-A-OH) obtained from Calbiochem (#123900) is used as a substrate. A final concentration of 0.6 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 30 μM ATP/γ^{33}P-ATP and 25 μM substrate. Compounds are added in DMSO solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. The reaction mixture is transferred to a phosphocellulose filter plate where the peptide binds and the unused ATP is washed away. After washing, scintillant is added and the incorporated activity measured by scintillation counting.

The % inhibition of the PKB activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

Following the protocol described above, the IC_{50} value of the compound of Example 1 has been found to be less than 5 μM.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 5

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50 mg of the compound with 197mg of lactose (BP) as diluent, and 3 mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

(iii) Injectable Formulation I

A parenteral composition for administration by injection can be prepared by dissolving a compound of the formula (I) (e.g. in a salt form) in water containing 10% propylene glycol to give a concentration of active compound of 1.5 % by weight. The solution is then sterilised by filtration, filled into an ampoule and sealed.

(iv) Injectable Formulation II

A parenteral composition for injection is prepared by dissolving in water a compound of the formula (I) (e.g. in salt form) (2 mg/ml) and mannitol (50 mg/ml), sterile filtering the solution and filling into sealable 1 ml vials or ampoules.

(iv) Subcutaneous Injection Formulation

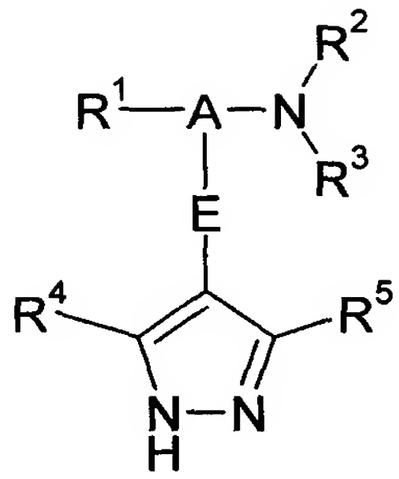
A composition for sub-cutaneous administration is prepared by mixing a compound of the formula (I) with pharmaceutical grade corn oil to give a concentration of 5 mg/ml. The composition is sterilised and filled into a suitable container.

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. A compound of the formula (I):



(I)

or a salt, solvate, tautomer or N-oxide thereof;

wherein:

A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group is replaced by a silicon atom, wherein the silicon atom is substituted with one or two substituents R^{15}, such that the silicon atom has a quaternary configuration;

each R^{15} is independently C_{1-4} alkyl, $O(C_{1-4}$ alkyl), phenoxy or hydroxy, wherein alkyl groups may be substituted with one or more halogen atoms and the phenoxy group may be substituted with one or more halogen or C_1-C_4 alkyl groups;

or one R^{15} group and the silicon atom to which it is attached and R^3 and the nitrogen to which it is attached form a 4 to 7 membered saturated heterocyclic ring;

and wherein the silicon atom is not adjacent the NR^2R^3 moiety;

and one of the carbon atoms in the linker group A may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α

with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl wherein the hydrocarbyl and acyl moieties are optionally substituted by one or more substituents selected from fluorine, hydroxy, amino, methylamino, dimethylamino and methoxy;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a cyclic group selected from an imidazole group and a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing the Si atom and/or a further heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, C_{1-5} saturated hydrocarbyloxy, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is a group R^{9a} or $(CH_2)R^{9a}$, wherein R^{9a} is a monocyclic or bicyclic group which may be carbocyclic or heterocyclic;

the carbocyclic group or heterocyclic group R^{9a} being optionally substituted by one or more substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more

substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

2. A compound according to claim 1 wherein the linker group A has a maximum chain length of 3 atoms extending between R^1 and NR^2R^3.

3. A compound according to claim 1 or claim 2 wherein the linker group A has a maximum chain length of 3 atoms extending between E and NR^2R^3.

4. A compound according to claim 3 wherein the linker group A has a chain length of 2 or 3 atoms extending between R^1 and NR^2R^3 and a chain length of 2 or 3 atoms extending between E and NR^2R^3.

5. A compound according to any one of claims 1 to 4, wherein there is only one atom of the linker group A between E and R^1.

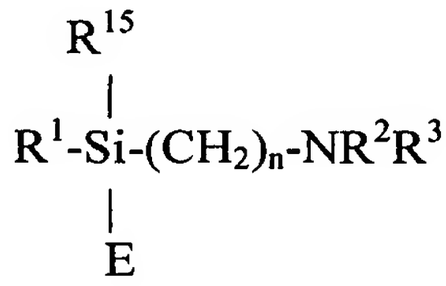
6. A compound according to any one of claims 1 to 5, wherein the silicon atom is linked directly to the group E and is substituted by a single group R^{15}.

7. A compound according to any one of claims 1 to 5, wherein R^{15} and R^3 together with the silicon and nitrogen atoms to which they are attached form a 5 to 7 membered saturated ring.

8. A compound according to claim 7, wherein R^{15} and R^3 together with the silicon and nitrogen atoms to which they are attached form a 6-membered ring.

9. A compound according to any one of claims 6 to 8, wherein R^{15} is C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy and there are 1, 2 or 3 further carbon atoms between the Si and the NR^2R^3 moiety.

10. A compound according to claim 9, wherein the linker A is of the form:

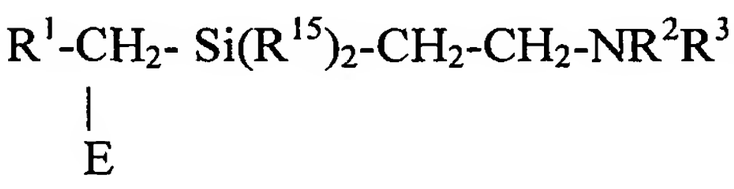


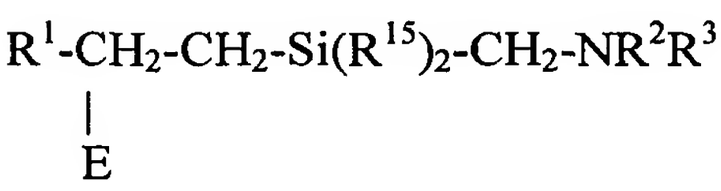
where n is 1, 2 or 3; and

where R^1, E and NR^2R^3 are not part of linker A but are included to show the position of the linker A within the compound of formula (I).

11. A compound according to any one of claims 1 to 5, wherein the silicon atom in the linker A is between the group E and the NR^2R^3 moiety but is not directly linked to the group E.

12. A compound according to claim 11, wherein the linker A is of the form:





where R^1, E and NR^2R^3 are not part of linker A but are included to show the position of the linker A within the compound of formula (I).

13. A compound according to any one of the preceding claims wherein R^1-A(E)-NR^2R^3 is a group selected from the groups A1 to A6 set out in Table 1 herein.

14. A compound according to any one of the preceding claims wherein E is a monocyclic group.

15. A compound according to any one of the preceding claims wherein E is an aryl or heteroaryl group.

16. A compound according to claim 15 wherein E is selected from optionally substituted phenyl, thiophene, furan, pyrimidine and pyridine groups.

17. A compound according to claim 16 wherein E is a phenyl group.

18. A compound according to any one of claims 1 to 17 wherein E is a non-aromatic monocyclic group selected from cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

19. A compound according to any one of the preceding claims wherein the group A and the pyrazole group are attached to the group E in a *meta* or *para* relative orientation; i.e. A and the pyrazole group are not attached to adjacent ring members of the group E.

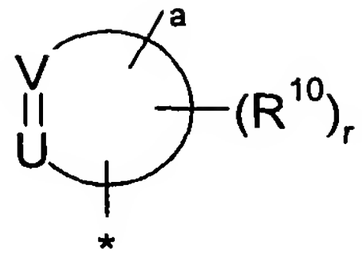
20. A compound according to claim 19 wherein E is selected from 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl.

21. A compound according to any one of the preceding claims wherein E is unsubstituted or has up to 4 substituents R^8 selected from hydroxy, oxo (when E is non-aromatic), chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

22. A compound according to claim 21 wherein E has 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent.

23. A compound according to claim 22 wherein E is unsubstituted.

24. A compound according to any one of the preceding claims wherein the group E is an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

r is 0, 1 or 2;

U is selected from N and CR^{12a}; and

V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten;

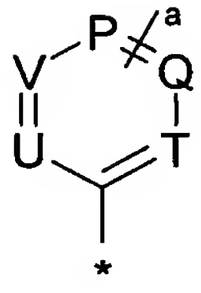
or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

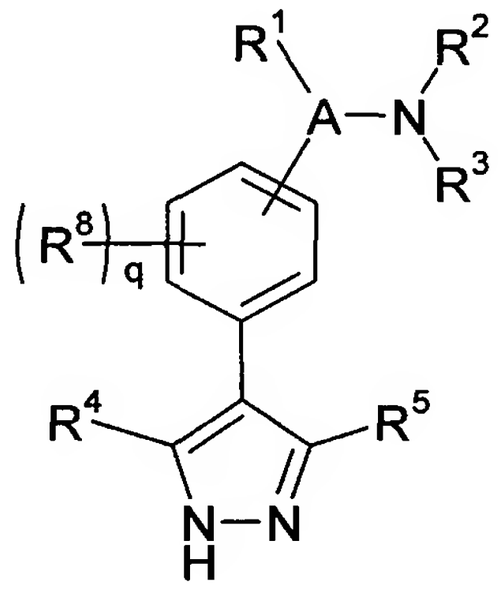
25. A compound according to claim 24 wherein E is represented by the formula:



where P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom.

26. A compound according to claim 25 wherein the group E is selected from groups B1 to B13 in Table 2.

27. A compound according to claim 20 having the formula (II):

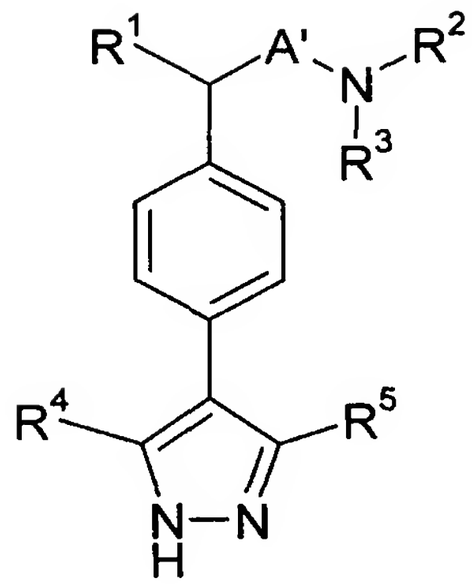


(II)

wherein the group A is attached to the *meta* or *para* position of the benzene ring and q is 0-4.

28. A compound according to claim 27 wherein q is 0, 1 or 2, preferably 0 or 1 and most preferably 0.

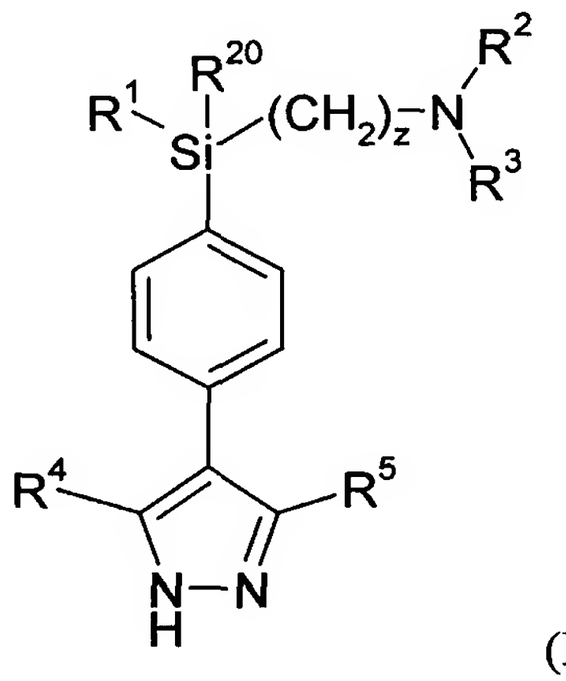
29. A compound according to claim 20 having the formula (III):



(III)

where A' is the residue of the group A and R^1 to R^5 are as defined in any one of the preceding claims.

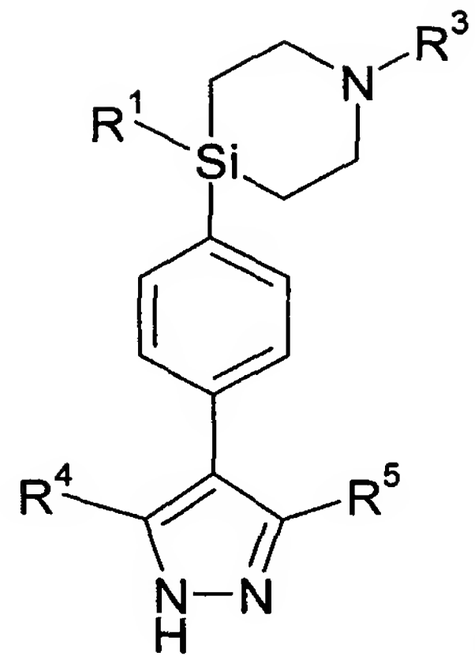
30. A compound according to claim 29 having the formula (IV):



(IV)

wherein z is 0, 1 or 2, R^{20} is selected from hydrogen, methyl, hydroxy and fluorine, provided that when z is 0, R^{20} is other than hydroxy.

31. A compound according to claim 29 having the formula (V):



(V)

32. A compound according to claim 31 wherein R^3 is selected from hydrogen and C_{1-4} hydrocarbyl, for example C_{1-4} alkyl such as methyl, ethyl and isopropyl, and more preferably R^3 is hydrogen.

33. A compound according to any one of the preceding claims wherein R^1 is selected from phenyl, naphthyl, thienyl, furan, pyrimidine and pyridine.

34. A compound according to claim 34 wherein R^1 is phenyl.

35. A compound according to any one of the preceding claims wherein R^1 is unsubstituted or bears one or more substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; $CONH_2$; nitro; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy, carboxy or hydroxy; C_{1-4} acylamino; benzoylamino; pyrrolidinocarbonyl; piperidinocarbonyl; morpholinocarbonyl; piperazinocarbonyl; five and six membered heteroaryl and heteroaryloxy groups containing one or two heteroatoms selected from N, O and S; phenyl; phenyl-C_{1-4} alkyl; phenyl-C_{1-4} alkoxy; heteroaryl-C_{1-4} alkyl; heteroaryl-C_{1-4} alkoxy and phenoxy, wherein the heteroaryl, heteroaryloxy, phenyl, phenyl-C_{1-4} alkyl, phenyl-C_{1-4} alkoxy, heteroaryl-C_{1-4} alkyl, heteroaryl-C_{1-4} alkoxy and phenoxy groups are each optionally substituted with 1, 2 or 3 substituents selected from C_{1-2} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, $CONH_2$, C_{1-2} hydrocarbyloxy and C_{1-2} hydrocarbyl each optionally substituted by methoxy or hydroxy.

36. A compound according to claim 35 wherein R^1 is unsubstituted or is substituted by up to 5 substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy; and five membered heteroaryl groups containing one or two heteroatoms selected from N, O and S, the heteroaryl groups being optionally substituted by one or more C_{1-4} alkyl substituents.

37. A compound according to claim 36 wherein R^1 is unsubstituted or is substituted by up to 5 substituents selected from hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

38. A compound according to claim 36 or claim 37 wherein R^1 is unsubstituted or is substituted by 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1or 2 substituents.

39. A compound according to claim 38 wherein the group R^1 has one or two substituents selected from fluorine, chlorine, trifluoromethyl, methyl and methoxy.

40. A compound according to claim 39 wherein R^1 is a mono-chlorophenyl or dichlorophenyl group.

41. A compound according to any one of the preceding claims wherein R^4 is selected from hydrogen and methyl.

42. A compound according to any one of the preceding claims wherein R^5 is selected from hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9b}$ and $NHCONHR^{9b}$ where R^{9b} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

43. A compound according to any one of the preceding claims wherein R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl.

44. A compound according to claim 43 wherein R^2 and R^3 are independently selected from hydrogen and methyl.

45. A compound according to claim 44 wherein R^2 and R^3 are both hydrogen.

46. A compound according to any one of the preceding claims having a molecular weight no greater than 1000, more usually less than 750, for example less than 700, or less than 650, or less than 600, or less than 550.

47. A compound according to claim 46 wherein the molecular weight is less than 525 and, for example, is 500 or less.

48. A compound of the formula (I) which is selected from the group consisting of:

4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
1-methyl-4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
4-(4-Chloro-phenyl)- 4'-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
4-phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-[1,4]azasilinane;
and salts, solvates, tautomers and N-oxides thereof.

49. A compound according to any one of the preceding claims in the form of a salt, solvate (such as a hydrate), ester or N-oxide.

50. A compound as defined in any one of claims 1 to 49 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

51. The use of a compound as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

52. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 49.

53. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective in inhibiting abnormal cell growth.

54. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKB activity.

55. A method of inhibiting a protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 49.

56. A method of modulating a cellular process by inhibiting the activity of a protein kinase B using a compound as defined in any one of claims 1 to 49.

57. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKB activity.

58. A compound as defined in any one of claims 1 to 49 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

59. The use of a compound as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

60. The use of a compound of the formula (I) as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth.

61. The use of a compound of the formula (I) as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease in which there is a disorder of proliferation, apoptosis or differentiation.

62. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 49.

63. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKA.

64. A method of inhibiting a protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 49.

65. A method of modulating a cellular process by inhibiting the activity of a protein kinase A using a compound as defined in any one of claims 1 to 44.

66. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKA activity.

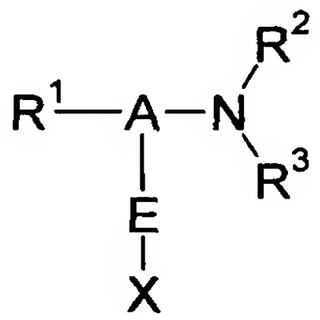
67. A method of inducing apoptosis in a cancer cell, which method comprises contacting the cancer cell with a compound as defined in any one of claims 1 to 49.

68. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 44 and a pharmaceutically acceptable carrier.

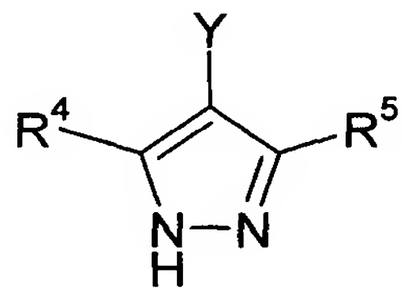
69. A compound as defined in any one of claims 1 to 49 for use in medicine.

70. A process for the preparation of a compound of the formula (I) as defined in any one of claims 1 to 49, which process comprises:

(a) the reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



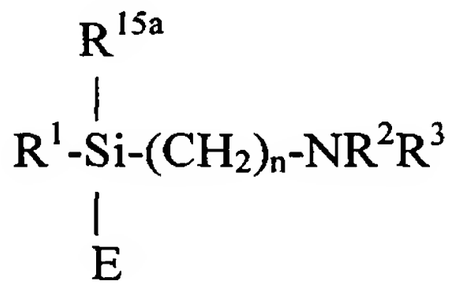
(X)



(XI)

wherein A, E, and R^1 to R^5 are as defined in any one of the preceding claims, one of the groups X and Y is selected from chlorine, bromine, iodine and trifluoromethanesulphonate, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue, in the presence of a palladium catalyst and a base;

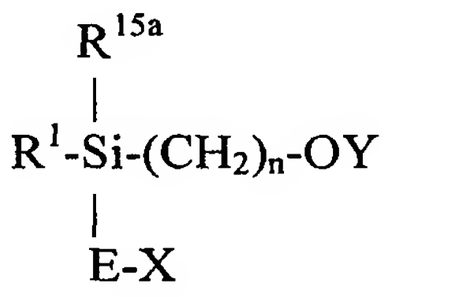
(b) when A is:



(where R^1, E and NR^2R^3 are not part of the group A but are included to show the position of the group A within the compound of formula (I));

and n is 2 or 3

by the reaction of a compound of formula (XL):



(XL)

where X, E, R^2, R^3 are as defined in formula (I), R^{15a} is C_1-C_4 alkyl and n is 2 or 3; with a compound of formula (XI) as defined above in the presence of an amine of formula (XX):

$$NHR^2R^3 \qquad (XX)$$

where R^2 and R^3 are as defined in formula (I); and optionally

(c) the conversion of one compound of the formula (I) into another compound of the formula (I).

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Application No: GB0512643.8 **Examiner:** Dr Simon Grand

Claims searched: 1-70 **Date of search:** 28 September 2005

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A,E	-	WO 2005/061463 A (ASTEX TECH.) See generic formula (I).
A	-	EP 1024138 A (YAMANOUCHI PHARMA.) See generic formula (I).

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[X] :

C2R

Worldwide search of patent documents classified in the following areas of the IPC[07]

C07F

The following online and other databases have been used in the preparation of this search report

ONLINE: EPODOC, WPI, CAS-ONLINE.